Neurology

OFFICIAL JOURNAL OF
THE AMERICAN ACADEMY OF NEUROLOGY

SEPTEMBER--1959
Volume 9 / Number 9

the tranquility of freedom

For the epileptic, what satisfaction can transcend the simple freedom to come and go . . . without fear. This precious gift of a normal life can be yours to give today, thanks in part to a finer knowledge of the disease—and improved drug therapy. Five anticonvulsants that have contributed much to the control of epilepsy are presented here. Won't you send for our detailed literature?

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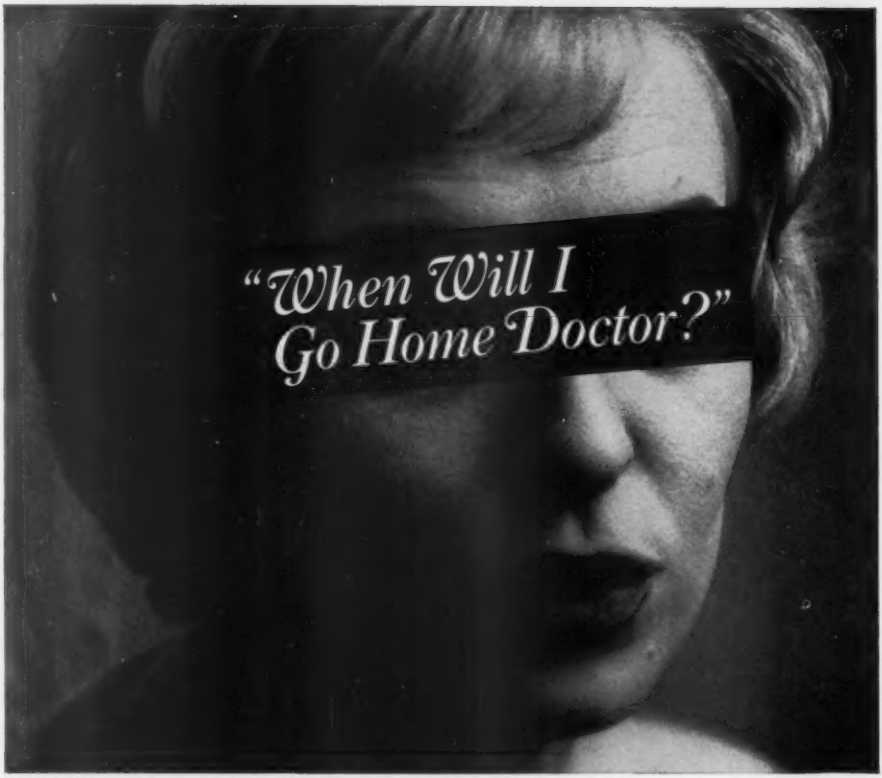

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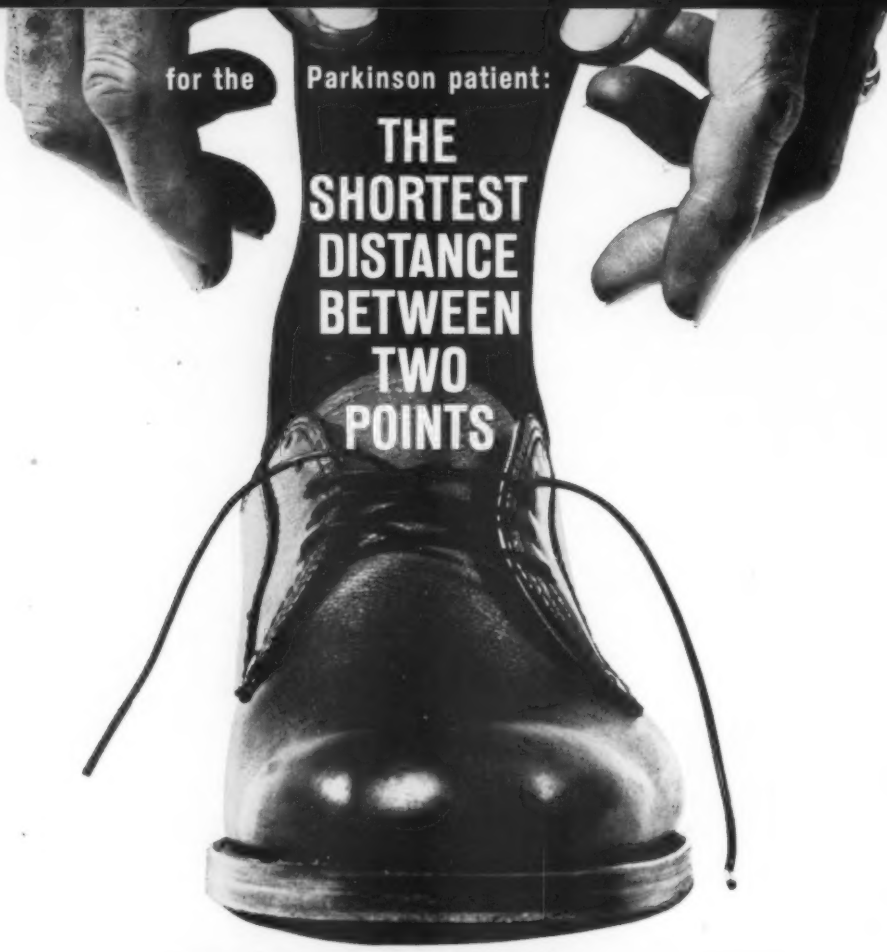
1. Goldman, D.: Am. J. M. Sc. 235:67 (Jan.) 1958. 2. Morehouse, W. G., and Freed, J. E.: Monographs on Therapy 3:32 (May) 1958. 3. Legar, Y.: Union Med. Canada 87:831 (July) 1958. 4. Bruckman, N. S.; Saunders, J. C., and Kline, N. S.: Monographs on Therapy 3:24 (May) 1958.



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1. Doshay, L. J.: M. Clin. North America 40:1401 (Sept.) 1956.
2. Doshay, L. J.: Current M. Dig. 22:11:49 (Nov.) 1955.
3. De Jong, R. N.: J. Michigan M. Soc. 57:722 (May) 1958.

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INFORMATION FOR *Authors*

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2. Doshay, L.J. et al.: J.A.M.A. 160:348 (Feb.) 1956.
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1. Lehrer, H. W., et al.: Northwest Med. 75:1249, 1955.
2. Smith, Richard T.: New York Med. 8:16, 1952.

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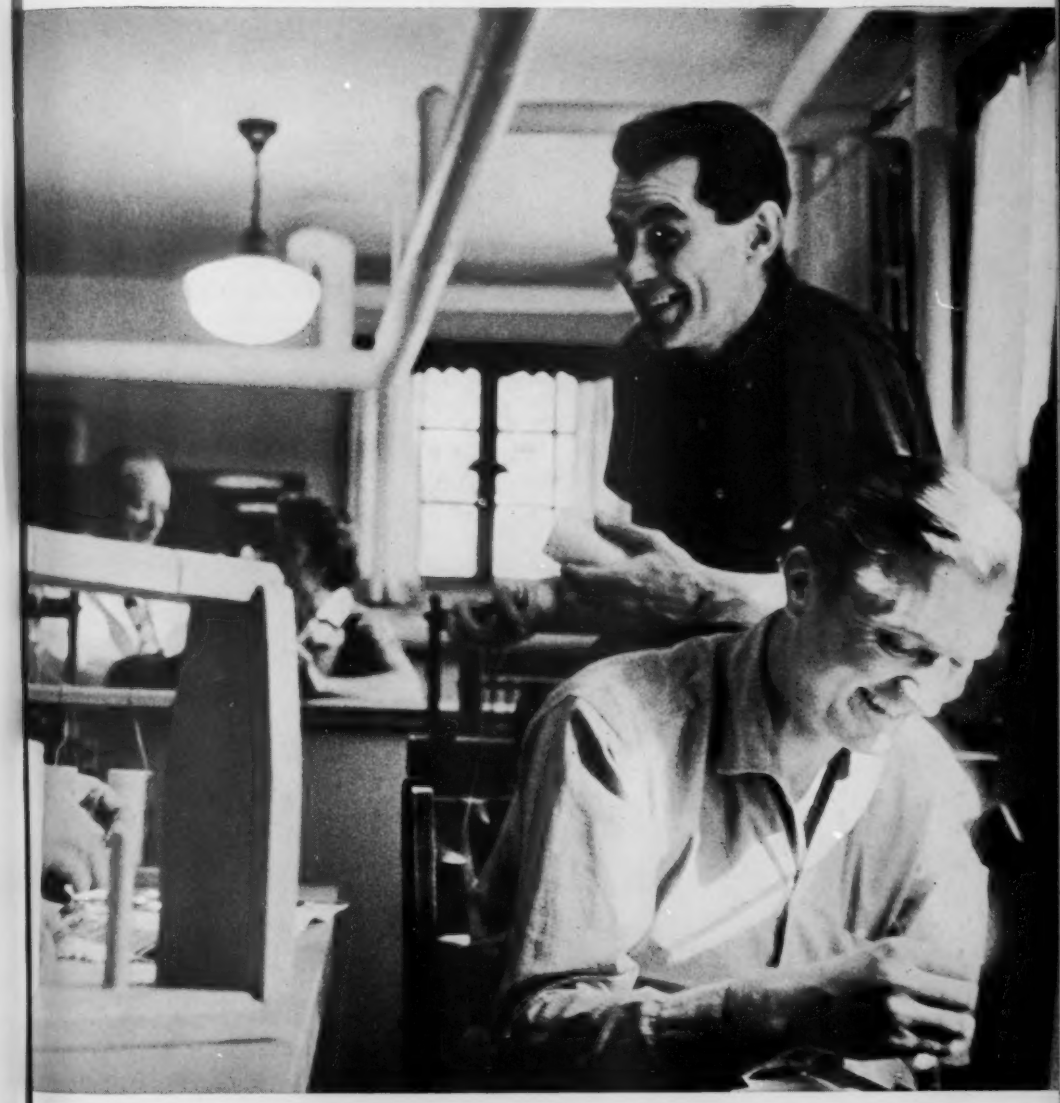

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Gunn, D.R.: The Role of Trifluoperazine in the Treatment of Refractory Mental Patients, in Trifluoperazine: Clinical and Pharmacological Aspects, Philadelphia, Lea & Febiger, 1958, pp. 47-53.

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Brooks, G.W.: Definitive Ataractic Therapy in the Rehabilitation of Chronic Schizophrenic Patients: A Preliminary Report on the Use of Trifluoperazine, *ibid.*, pp. 54-61.

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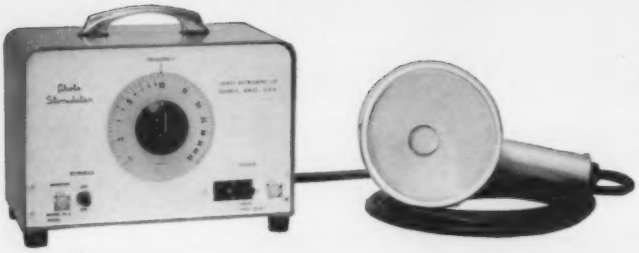

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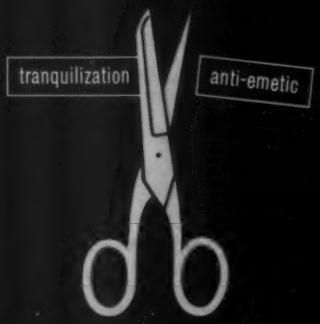

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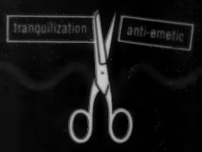

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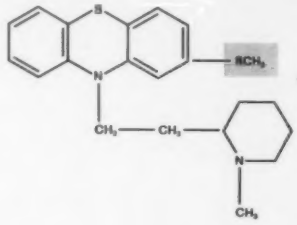

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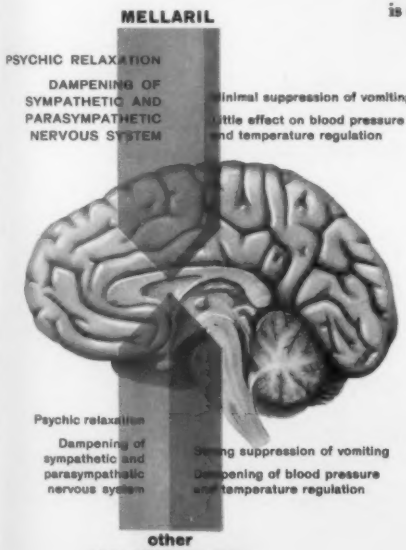
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Dampening of sympathetic and parasympathetic nervous system
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EXTREMELY SATISFACTORY "... produced extremely satisfactory results in the broad therapeutic range represented in this series."[3]

POTENT AGENT "... appears to be a potent agent in the symptomatic management of a variety of psychiatric states."[4]

MAJOR ADDITION TO THERAPEUTICS "This drug appears to represent a major addition to the safe and effective treatment of a wide range of psychological disturbances seen daily in the clinics or by the general practitioner."[1]

AN ACTIVE AGENT "Thioridazine is an active therapeutic agent.... It is effective in a variety of psychiatric disorders, including schizophrenic reactions.... The drug is particularly advantageous for a group of schizophrenic patients who are sometimes made worse by other phenothiazine derivatives or Rauwolfia alkaloids. It should also be suitable for treating patients with psychoneuroses and chronic brain syndrome."[6]

EVEN IN VERY SEVERE CASES "Of the 152 patients treated 25 have been released and they have not suffered a relapse. This proportion is significant if we stop to consider that we are dealing only with acute cases which had been considered hopeless and obviously destined to finish their days in an asylum."[7]

EXCELLENT THERAPEUTIC RESPONSE "Patients with emotional tensions resulting from the stress and strain of life... were treated with Mellaril at the dosage level of 10 mg. three times daily. In 94 such patients, 83 obtained an excellent therapeutic response."[8]

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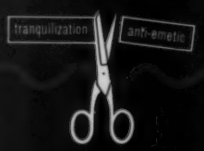

"...extremely satisfactory results..." in a clinical spectrum ranging from minor nervous disorders to severe psychotic disturbances[3]

RESULTS WITH MELLARIL IN 194 PATIENTS[3]

ACUTE PSYCHOTICS	CHRONIC PSYCHOTICS	NEUROTICS
83% satisfactory effect	68% satisfactory effect	57% satisfactory effect
Some cases had complete remission of symptoms. Most were able to return home to useful occupations.	Relief of symptoms in cases permitted easier management and a return to a more or less useful life.	Some cases, complete relief of symptoms. Other cases, partial relief of symptoms.

RESULTS WITH MELLARIL IN PATIENTS PREVIOUSLY TREATED WITH OTHER TRANQUILIZERS[3]

DIAGNOSTIC CATEGORY	IMPROVED %	VERY SATISFACTORY %	SATISFACTORY %	UNSATISFACTORY %
SCHIZOPHRENIA				
Acute	89	61	28	11
Chronic paranoid	84.2	31.6	52.6	15.8
Chronic, other	73.9	21.7	52.2	26.1
Residual	57.1	9.5	47.6	42.9
CHRONIC BRAIN SYNDROME	66.6	33.3	33.3	33.3
CHRONIC PSYCHONEUROSIS	62.5	12.5	50	37.5
CHRONIC PSYCHOSOMATIC DISORDERS	75	25	50	25

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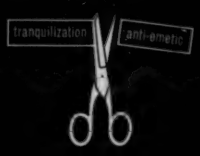

a guide to administration and dosage

Dosage ranges from 10 mg. three or four times a day in milder situations to 25 mg. three or four times a day for more disturbed patients. In ambulatory psychiatric out-patients, dosages of 50 to 100 mg. three or four times a day have been found adequate. For severely disturbed hospitalized psychotics, dosages of 200 to 300 mg. three times a day may be administered.

Dosage must be individualized according to the condition and degree of response. In all cases, the smallest effective dosage should be determined for each patient.

INDICATION	USUAL STARTING DOSE	TOTAL DAILY DOSAGE RANGE
	ADULTS	
Mental and Emotional Disturbances:		
MILD—where anxiety, apprehension and tension are present	10 mg. t.i.d.	20-60 mg.
MODERATE—where agitation exists in psychoneurosis, alcoholism, intractable pain, senility, etc.	25 mg. t.i.d.	50-200 mg.
SEVERE—in agitated psychotic states as schizophrenia, manic depressive, toxic psychoses, etc.:		
Ambulatory	100 mg. t.i.d.	200-400 mg.
Hospitalized	100 mg. t.i.d.	200-800 mg.
	CHILDREN	
BEHAVIOR PROBLEMS IN CHILDREN	10 mg. t.i.d.	20-40 mg.

PRECAUTIONS: Although possessing a unique structure and a selectivity of action which broadens its therapeutic ratio, the physician should be alert to the possibility of untoward reactions in certain susceptible individuals. In particular, he should watch for potential hemopoieti depression, jaundice or orthostatic hypotension. As wit other phenothiazines, Mellaril is contraindicated i severely depressed or comatose states from any cause.

SUPPLIED: MELLARIL Tablets, 10 mg., 25 mg., 100 mg. Bottles of 100.

1. Ostfeld, A. M.: Scientific Exhibit, American Academy of General Practice, San Francisco, April 6-9, 1959. 2. Kinross-Wright, V. J.: Lecture, Clinic Meeting, American Medical Association, Minneapolis, Dec. 4, 1958. 3. Kinross-Wright, V. J.: Scientific Exhibit, Clinical Meeting, American Medical Associ ation, Minneapolis, Dec. 2-5, 1958. 4. Cohen, S.: TP-21, a new phenothiazine, Am. J. Psychiat. *115*:358, Oct. 1958. 5. Glueck, B.: Scientific Exhibit, American Psychiatric Association, Philadelphia, April 27-May 1, 1959. 6. Hollister, L. E., and Macdonald, B. F.: Presented at California Medical Association; Section on Psychiatry, San Francisco, Feb. 25, 1959. 7. Remy, M.: Schweiz. med. Wchnschr. *88*:1221, Nov. 29, 1958. 8. Freed, S. C., in discussion on Thioridazine (Mellaril) in Psychiatric Patients, Hollister, L. E., and Macdonald, B. F., presented at California Medical Association; Section on Psychiatry, San Francisco, Feb. 25, 1959.

- controls neurotic and psychotic patients with anxiety, apprehension, nervous tension
- virtual absence of jaundice, parkinsonism, photosensitivity, dermatitis
- minimal sedation and drowsiness
- does not mask organic conditions such as brain tumors, intestinal obstruction, etc., because of lack of anti-emetic action
- increased specificity of action results in greater safety at all dosage levels

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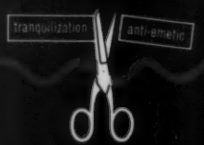

Dynamic Myelography

These two radiographs of the same patient demonstrate the bulging of the annulus fibrosus during hyperextension and flexion, respectively, of the vertebral column. 30 cc of ***Pantopaque*** contrast medium was used. Note how this technique permits visualization of the posterior surface of the vertebral canal.

"PANTOPAQUE" *is the registered trademark under which all leading x-ray dealers supply the compound ethyl iodophenylundecylate, which is synthesized by the Research Laboratories of Eastman Kodak Company and prepared as the myelographic contrast medium Iophendylate Injection, U.S.P., by Lafayette Pharmacal Inc. The trademark serves to indicate to the radiologist continuity of experience in the manufacture of this medium.*

new...simple tablet therapy corrects mild to severe depressions rapidly and safely

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restores the depressed, despondent or suicidal patient[1-3]

rapidly: Antidepressant activity apparent within the first few days; self-deprecatory feelings, sadness, repetitive thinking, psychomotor inhibition and suicidal ideation rapidly subside; complete remission usually occurs within 2 to 6 weeks.

correctively: Helps remove the depression itself, does not merely mask the symptoms. Nardil is a potent, but well tolerated, monoamine oxidase inhibitor with preferential distribution to the brain—not the liver—which readily passes the blood-brain barrier. Excellent antidepressant therapy when, in your judgment, ECT may be undesirable or unnecessary. Nardil "...clearly compares to electroconvulsive therapy in scope, rapidity of action and freedom from serious side effects."[1]

with low toxicity: No recorded incident of toxicity to liver, kidneys or blood[1-3] in thousands of cases to date. Side effects are only mild and transient. An occasional postural hypotension is managed easily and traditionally.

Indications: Nardil has been found to produce its best clinical results in mild to severe depressions of either the larval or overt type, and in depressions associated with chronic diseases such as angina pectoris and rheumatoid arthritis.

Nardil has also been found to improve the depressed phase of affective (manic-depressive) psychosis. It is also of value in relieving the depression of catatonic schizophrenics, although not affecting the psychosis *per se*.

Side Effects: Occasional side effects which have been reported include postural hypotension in those patients whose pretreatment pressure is low, nausea, ankle edema, delayed micturition and constipation. These can be adequately managed by appropriate adjunctive therapy, or will abate as dosage is reduced to the maintenance level.

Caution: Even though there have been no significant reports of toxic effects on the liver with the use of Nardil, as a matter of caution, patients should be carefully followed with liver profile studies and the drug should be withheld or used with extreme care where the patient has a history of liver disease or where liver damage is present. Also, hypotensive patients should be closely supervised.

Dosage: Starting dose is one 15 mg. tablet three times a day. Improvement is usually seen within one week. After maximum benefit is achieved, the dosage should be reduced slowly over a period of several weeks to a maintenance level as low as 15 mg. a day. For the occasional patient who does not respond to the above starting dose an additional one or two tablets may be given at bedtime.

Supplied: 15 mg. orange-coated tablets, bottles of 100.

References: **1.** Sainz, A.: The Phrenopraxic Activity of a Non-noxious Antidepressant, *Ann. New York Acad. Sc.* (in press) 1959. **2.** Thal, N.: Cumulative Index of Antidepressant Medications, *Dis. Nerv. System* 20:197 (May) 1959. **3.** Saunders, J. C.; Roukema, R. W.; Kline, N. S., and Bailey, S. d'A.: Clinical Results with Phenelzine, *Am. J. Psychiat.* (in press) 1959.

WARNER CHILCOTT

MORRIS PLAINS, N.J.

To facilitate psychotherapy in the emotionally disturbed child, and to enable him to lead a stable life during such therapy, adjunctive treatment with PROZINE is often advantageous. In reporting on 176 disturbed children who received PROZINE, Ehrmantraut et al.[1] found that 85.8 per cent showed moderate to marked improvement in behavior reactions and adjustment to institutional care.

PROZINE, designed for the treatment of moderate to severe emotional disturbances, helps control psychomotor agitation as well as anxiety and tension.

1. Ehrmantraut, W., et al.: Scientific Exhibit Presented at the District of Columbia Medical Society Meeting, Nov. 24, 1958, Washington, D.C.

controlled: an acute behavioral problem

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Neurology Volume 9 • Number 9

Development of cerebral atherosclerosis in various age groups

John Moossy, M.D.

IN RECENT YEARS, studies of the pathology of cerebral atherosclerosis have been numerous. However, all workers realize that cerebral atherosclerosis is but one part of the larger problem of systemic atherosclerosis and, controversial though the subject may be, more attention should be directed to the pathogenesis and phasic development of atherosclerotic lesions.

Hence, some investigation of the morphologic patterns of cerebral atherosclerosis in various age groups was felt warranted. The cerebral vessels have been studied in 122 patients to date, ranging in age from newborn to 93 years, as part of a larger continuing study of the pathology and natural history of atherosclerosis.[1] Preliminary data relating cerebral atherosclerosis to aortic and coronary forms of the disease were recently discussed by Holman and Moossy.[2]

MATERIALS AND METHODS

The intracranial portions of the internal carotid and basilar-vertebral arterial systems were removed from 122 patients who came to autopsy on the Louisiana State University pathology service at Charity Hospital in New Orleans. Certain characteristics of this autopsy population are discussed elsewhere.[1]

The cases were unselected. All brains were fixed in 10% formalin for two weeks, then dissected in the routine fashion with special attention to small areas of encephalomalacia, recent or old, or other signs of cerebrovascular disease commonly attributed to atherosclerosis or hypertension. The arteries were dissected from the fresh brain at the time of autopsy, opened longitudinally along their ventral surfaces, and carefully flattened on cardboard with intimal surfaces exposed. No attempt was made to open branches less than 1 mm. in diameter. During the dissection, intimal surfaces were moistened with a small pad of cotton soaked with 10% formalin. The vessels were then fixed in formalin for twenty-four to forty-eight hours, stained in gross with Sudan IV, mounted on celluloid, and preserved in clear plastic bags containing a small amount of fixative with thymol. This technic, with minor modifications, has previously been used chiefly for the aorta and coronary arteries.[3,4]

Intimal surfaces were studied with the naked eye and with the aid of a dissecting

From the Division of Neurology and Department of Pathology, Louisiana State University School of Medicine, and the Charity Hospital of Louisiana, New Orleans.
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Read at the eleventh annual meeting of the American Academy of Neurology, Los Angeles, April 16, 1959.

TABLE 1

CEREBRAL ATHEROSCLEROSIS

TABULATION OF 122 CASES BY AGE, SEX, AND RACE

Age in years	White M	White F	Negro M	Negro F	Total
0 - 9	2	2	6	7	17
10 - 19	1	1	0	4	6
20 - 29	0	0	0	2	2
30 - 39	2	0	2	6	10
40 - 49	1	0	3	5	9
50 - 59	5	1	11	7	24
60 - 69	5	2	5	11	23
70 - 79	11	6	2	3	22
80 - 89	1	1	2	2	6
90 +	0	0	2	1	3
Total	28	13	33	48	122

microscope. The total intimal surface available for examination was measured in square millimeters. The amount of intimal surface stained red with Sudan IV as well as that involved with all stages of atherosclerosis was measured, and the percentage surface involvement was calculated. Data for individual arteries, variations in anatomic patterns, and incidence of nonatherosclerotic lesions and of ruptured and unruptured aneurysms will be the subject of a future publication.

After grading, representative specimens from each decade were photographed and samples for microscopic sections were taken. Frozen sections were stained with Sudan IV, and paraffin-embedded sections were stained with

TABLE 2

CEREBRAL ATHEROSCLEROSIS

SUMMARY OF DATA IN 122 CASES BY DECADES

Age Race Sex	Total % surface involved	Arterial lesions: Fatty streaks	Arterial lesions: Fibrous plaques	Complicated lesions: Hem.	Complicated lesions: Thromb.	Complicated lesions: Ca.	Parenchymal lesions: Fatal	Parenchymal lesions: Nonfatal
0 - 9 years								
No lesions found								
10 - 19 years								
No lesions found								
20 - 29 years								
29 CF	3	+	+	−	−	−	−	−
26 CF	4	+	+	−	−	−	−	−
30 - 39 years								
36 WM	7	+	+	−	−	−	−	−
37 CF	1	+	+	−	−	−	−	−
34 WM	17	+	+	−	−	−	−	−
35 CF	3	+	+	−	−	−	−	−
31 CF*	1	+	+	−	−	−	+	−
37 CM	26	+	+	−	−	−	+	+
35 CF	12	+	+	−	−	−	−	−
30 CF	5	−	+	−	−	−	−	−
36 CM	2	+	+	−	−	−	−	+
30 CF	1	+	+	−	−	+	−	−
40 - 49 years								
48 CM	43	+	+	−	−	−	−	+
48 WM	2	+	+	−	−	−	−	−
46 CF	10	+	+	−	−	−	−	−
47 CF	31	−	+	−	−	−	+	−
44 CM	27	−	+	−	−	−	−	−
42 CF	2	+	+	−	−	−	−	−
48 CM	45	−	+	−	−	+	−	+
47 CF	5	+	+	−	−	−	−	−
49 CF	11	−	+	−	−	−	−	−
50 - 59 years								
57 WM	44	+	+	−	−	−	+	−
58 CM	48	+	+	−	−	−	+	+
54 CM	10	+	+	−	−	−	−	−
58 CM	55	+	+	−	−	−	−	+
50 CF	13	−	+	−	−	−	−	−
57 CM	7	+	+	−	−	−	−	−
57 CM**	77	+	+	+	+	+	+	+
53 WM	17	−	+	−	−	+	−	−
52 CF	36	−	+	−	−	−	−	+
55 CF	10	+	+	−	−	−	−	−
58 WM	15	+	+	−	−	−	−	−
59 WF	13	+	+	−	−	−	−	−
53 CF	16	+	+	−	−	−	−	−
58 CM	3	+	+	−	−	−	−	−
54 CF	14	−	+	−	−	−	−	+

TABLE 2 (continued)

CEREBRAL ATHEROSCLEROSIS

SUMMARY OF DATA IN 122 CASES BY DECADES

Age Race Sex	Total % surface involved	Arterial lesions					Parenchymal lesions	
		Fatty streaks	Fibrous plaques	Complicated lesions				
				Hem.	Thromb.	Ca.	Fatal	Nonfatal
50 CM	12	+	+	−	−	−	−	−
57 WM	8	+	+	−	−	+	−	−
52 CM	13	+	+	−	−	+	−	−
59 CM	11	+	+	−	−	−	−	−
52 WM	18	+	+	−	−	−	−	−
57 CF	26	+	+	−	−	−	+	+
58 CM	11	+	+	−	−	−	−	−
58 CM	35	+	+	−	−	−	−	+
54 CF	14	+	+	−	−	+	−	−
60 - 69 years								
65 CF	18	−	+	−	−	−	−	−
67 CF	30	+	+	−	−	−	−	+
67 CF	38	+	+	−	−	−	−	−
65 CF	9	+	+	−	−	−	−	−
65 CM	5	+	+	−	−	−	−	−
61 CF	31	−	+	−	−	−	−	−
65 CF	43	−	+	−	−	−	−	−
62 CF	70	+	+	−	−	−	−	+
69 WF	14	+	+	−	−	−	−	−
63 WM	14	+	+	−	−	−	−	−
69 CM	3	−	+	−	−	−	−	−
61 WM	17	−	+	−	−	−	−	−
68 CF	35	+	+	−	−	−	−	+
68 WM	25	+	+	−	−	−	−	−
63 WM	8	−	+	−	−	−	−	+
63 CF	36	+	+	−	−	+	−	+
64 CM	42	+	+	−	−	+	+	−
69 CM	8	+	+	−	+	−	+	−
63 CF	9	+	+	−	−	−	−	−
64 CF	20	+	+	−	−	−	+	−
63 WF	9	+	+	−	−	−	−	−
66 WM	24	+	+	−	−	−	−	+
60 CM	32	+	+	−	−	−	−	−
70 - 79 years								
73 WF	60	−	+	−	−	−	−	+
77 CF	77	−	+	−	−	−	−	+
79 WF	23	+	+	−	−	−	−	+
78 WM	19	+	+	−	−	−	−	−
75 WM	26	−	+	−	−	−	−	+
78 WF	42	+	+	−	−	−	−	+
76 WM	81	−	+	−	+	−	−	+
73 WM	17	+	+	−	−	−	−	−
72 CM	15	+	+	−	−	−	−	+
74 WF	17	+	+	−	−	−	−	−
71 WF	18	+	+	−	−	+	−	−
76 CF	6	−	+	−	−	−	−	−
78 CF	32	+	+	−	−	−	−	−
73 WM	10	+	+	−	+	−	+	−
75 WM	20	+	+	−	−	+	−	+
74 WF	12	+	+	−	−	−	−	−
73 WM	9	+	+	−	−	−	−	−
78 WM	49	+	+	−	−	+	−	+
71 WM	3	+	+	−	−	−	−	−
70 WM	73	+	+	−	−	−	−	−
70 CM	19	+	+	−	−	+	−	+
76 WM	32	+	+	−	−	+	−	−
80 - 89 years								
88 WF	17	+	+	−	−	−	−	−
85 WM	30	+	+	−	−	−	−	−
80 CF	72	−	+	−	−	−	−	+
82 CM	37	+	+	−	−	+	−	+
80 CF	40	+	+	−	−	−	−	−
83 CM	80	+	+	−	−	+	−	+
90+								
90 CM	31	+	+	−	−	−	+	+
92 CF	67	+	+	−	−	+	−	+
93 CM	17	+	+	−	−	−	−	−

* See text
** See text

C = colored
W = white

F = female
M = male

Hem. = hemorrhage in plaque
Thromb. = thrombosis on plaque
Ca. = calcification

hematoxylin-eosin and Verhoeff's elastic tissue stains.

RESULTS

The cases in this series are tabulated by age, race, and sex in Table I. In Table 2, individual cases are listed within each decade. These tabulations show some obvious deficiencies, especially in the 10 to 19 and 20 to 29 age groups and in the white race. All 23 patients less than 20 years of age were negative for any stage of atherosclerosis. The youngest patient with evidence of cerebral artery involvement was a 26-year-old colored female. From the third decade onward, all patients showed some degree of cerebral atherosclerosis, though the range of variation in quantitative severity was quite great within the fourth through tenth decades and not necessarily correlated with chronologic age (Table 2). Examples of the cerebral vessel dissections are shown in Figures 1 through 4. The earliest lesions appeared to be lipid or fatty streaks, intensely sudanophilic linear deposits, or small oval-shaped masses in the intima. These streaks were usually only a few millimeters in length and width.

The earliest sites of deposition were the internal carotid and verterbral arteries, followed by the basilar artery and middle cerebral vessels. The anterior cerebrals and cerebellar arteries showed less frequent and less extensive involvement. The posterior inferior cerebellar artery was the earliest of the cerebellar vessels affected and, almost always, more severely than the others. In vessels other than the carotids or vertebrals, lesions appeared earliest near bifurcations or the ostia of branches.

Fibrous plaque formation was evident in some vessels in all age groups showing lesions, and most of the involved areas were mixtures of fibrous tissue and fatty streaks. Fibrous plaques were grossly gray to milky white in color, larger than simple fatty streaks, elevated, and firm to palpation. They often were surrounded partially or completely by a bright red lipid or fatty streak. It is interesting that we were unable to detect any purely fibrous connective tissue; that is, every lesion contained some evidence of lipid deposition either grossly or microscopically.

There was calcification within the intimal plaques in 17 cases, invariably limited to the internal carotid and vertebral arteries.

Hemorrhage within a plaque was detected only once, either by naked eye inspection or with the dissecting microscope, in a plaque in the left vertebral artery of a 57-year-old colored male with 77% of the total intimal surface involved and severe cerebral vascular complications (** in Table 2). In the microscopic sections, hemosiderin-laden phagocytes were occasionally seen in small numbers in the base or at the margins of lesions where no hemorrhage had been apparent grossly.

Thromboses were superimposed on atherosclerotic plaques in only 4 cases. In 12 cases, cerebral vascular lesions—encephalomalacia or hemorrhage—were severe enough to be considered the cause of death or one of the causes of death (Table 2). In this group, 5 also had cerebral vascular lesions not considered significant as a cause of death (Table 2), usually small areas of old encephalomalacia or hemorrhage. In 27 patients, old, small parenchymal lesions alone were present. In the group of patients with anatomic evidence of tissue damage presumably related to atherosclerosis, the percentage involvement of the intracranial vessels was usually above 20%. Most of these patients were in the sixth decade or beyond. One patient (* in Table 2) had only 1% total intimal surface involvement but died of a massive hemorrhage in the corpus striatum and temporal lobe. The location of the hemorrhage was somewhat atypical, and there was no clinical or pathologic evidence of hypertension. Careful gross and microscopic studies of the brain failed to disclose an aneurysm, vascular malformation, or arteritis. We suspect that a small aneurysm, greatly destroyed and distorted by rupture, was the most likely explanation in this case.

Another obvious deficiency in this material, evident at this point, concerns the state of the extracranial portions of the internal carotid and vertebral arterial systems. With only 4 thromboses and such a high incidence of parenchymal lesions, one wonders about the state of the extracranial cerebral circulation. Of course, other hemodynamic considerations enter here, too, such as the cumulative effects produced by numerous areas of both stenosis in small vessels and ectasias in the larger ves-

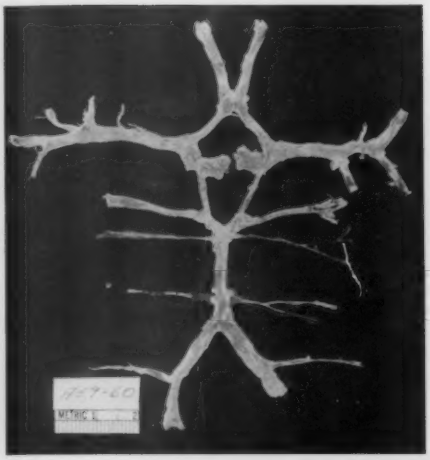

Fig. 1. Vessels of 1-year-old colored male. Total intimal surface involved = 0

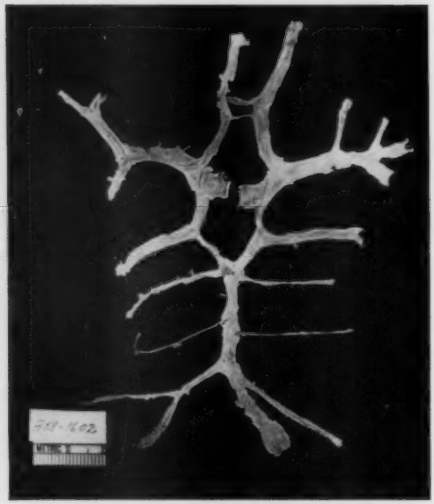

Fig. 2. Vessels of 30-year-old colored female. Total intimal surface involved = 5%, exclusively in internal carotids, vertebrals, and basilar artery.

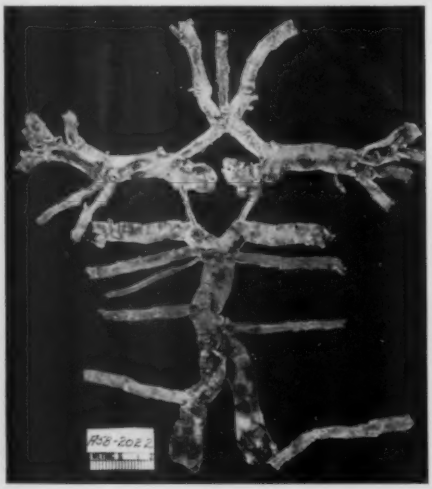

Fig. 3. Vessels of 57-year-old colored female. Total intimal surface involved = 26%

Fig. 4. Vessels of 92-year-old-colored female. Total intimal surface involved = 67%

sels caused by atherosclerotic distortion of their walls. Other factors have been discussed in a previous publication.[2]

DISCUSSION

Previous work on the morphology of cerebral atherosclerotic lesions has generally taken the form of clinicopathologic correlative study and

dealt with patients in whom clinical disease provided the chief impetus for investigation.[5] Appraisal of extracranial vascular disease affecting the brain has been the subject of much recent work.[6–8] The relationship of cerebral disease to atherosclerosis in other sites, such as the coronary arteries, aorta, and peripheral vessels, is another area of new interest, and the scarcity of data has been well recognized.[9] Winter and associates[10] recently have studied correlations between atherosclerosis of the intracranial portion of the internal carotid artery in women, their ages, and the degree of coronary artery disease. Young and coworkers[11] examined the coronary and cerebral vessels in 37 autopsied cases and found significant correlations. They found coronary lesions, on the average, more advanced than those in cerebral vessels within a given age group.

In all the investigations referred to above, either dissection, verbal description[5] and diagrams of the relative amount of lumen compromised utilizing cross sections of the arteries at various points in their course,[6,8] or a grading system based on cross sections[7,10,11] have been employed. Wolkoff[12] of Anitschow's laboratory studied the cerebral arteries of 98 patients between the ages of 2 and 81 years. Vessels were opened longitudinally in situ and the brain and vessels fixed in formalin and stained with Sudan III. The first lesions of atherosclerosis, "fatty spots," were not noted until the third decade, and it was felt that, although cerebral lesions corresponded to those found in the aorta and coronaries, there were some important differences, chiefly a development later in life of the cerebral form.

The present series closely resembles Wolkoff's in that many of the morphologic features in the 1933 publication are confirmed. We have attempted to add a practical quantitative approach; work is currently in progress on correlation between the quantitative degree of atherosclerosis in the cerebral and coronary arteries and the aorta in the same patients. Preliminary data in this area[2] indicates that aortic lesions are first evident with fatty streaks in the first decade and that coronary lesions become evident in the second decade and cerebral vessel involvement in the third. In each decade, aortic lesions are, on the average, quantitatively greater and coronary arteries follow; generally, cerebral vascular involvement appears to be the least severe. Some exceptions have been encountered, and, as mentioned previously, there is a great range of variation within each age group. The phasic or sequential development of lesions from lipid or fatty streaks to fibrous plaques to complicated lesion is more clearly seen and distinctions more sharply made in the aorta and coronary arteries than in the cerebral vessels, where most, though not all, of the lesions appear as mixed, fatty streaks and fibrous tissue, that is, as fibrous plaques.

SUMMARY

The intracranial vessels of 122 patients and the development and morphology of atherosclerotic lesions in various age groups have been studied. Quantitative estimates of cerebral atherosclerosis have been attempted.

Some comments about associated pathologic lesions attributable to atherosclerosis and about the relationship of cerebral, coronary, and aortic atherosclerosis have been made.

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Clinical and electroencephalographic considerations in the diagnosis of carotid artery occlusion

A review of 35 verified cases

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In 1937, when Moniz and his associates reported the first 4 cases of internal carotid thrombosis to be demonstrated by arteriography, they noted that the initial clinical suspicion had been an intracranial mass lesion.[1] Since that time, as the result of increasingly greater utilization of the arteriographic technic, numerous cases of carotid occlusive disease have been reported and diverse associated syndromes have been described.[2–5] In spite of this increasing knowledge, the prearteriographic diagnosis of this fairly common disease[6–8] continues, in many cases, to be brain tumor.[2,9] Neurologists have, therefore, turned to electroencephalography for diagnostic assistance and have reported abnormal records of various types in most cases.[10–14] One group, however, has reported normal records in a majority of cases so studied.[2]

Other electroencephalographic studies have stressed the frequency of normal records in patients with cerebrovascular occlusion as compared to patients with brain tumor and have also noted that, when abnormal records were found, reversion to normal usually occurred within two or three weeks.[15,16] In experimental animals subjected to middle cerebral artery occlusion, a similar disappearance of "abnormalities of localizing value" was noted after one week.[17]

The implication of the reported data has been that, unlike cerebrovascular disease in general, carotid occlusive disease causes unique and varied electroencephalographic and clinical characteristics. This study deals with a large series of verified cases of partial and complete carotid artery occlusion emphasizing the nature, extent, and duration of electroencephalographic abnormalities and their relationship to the clinical picture.

METHOD

A report is made of 35 patients with carotid occlusive disease. These represent all patients with this condition treated at the Neurological Institute of New York between 1949 and 1957 whose studies included at least 1 electroencephalogram and verification of the diagnosis by arteriography (31 patients), postmortem examination (2 patients), angiocardiography (1 patient), and operation (1 patient).

An 8-channel Grass electroencephalograph was employed. The examination consisted of monopolar and bipolar recordings from 18 scalp areas. Sleep activation was not employed. Hyperventilation was utilized in all cooperative patients. Postural tilting during the recording was performed in the follow-up study of 7 patients.

Because of the variable course of the disease, each electroencephalographic study (Table 1) has been dated from the time of the most recent exacerbation of symptoms rather than from the time of onset of the initial symptoms, a period which in many patients appeared to have antedated hospitalization from one to several years.

A brief classification system (Tables 1 to 3) has been employed. A normal record exhib-

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TABLE 1

CASE SUMMARIES: MAJOR CLINICAL AND ELECTROENCEPHALOGRAPHIC FINDINGS

Case Age, Sex	*Site and nature of occlusion*	*Verification*	*Clinical features*	*Severity of neurologic deficit at time of EEG*	*Duration of most recent symptoms at time of EEG*	*EEG description* (See text for definition of terms)
1. M.G. 186908 54 F	Left internal carotid. Recanalized at bifurcation.	Left common carotid arteriogram	Organic mental syndrome, 4 years. Paralysis right arm, six days.	Marked	12 days	S2 left lateral; S3 left temporal
2. B.N. 174109 62 M	Left internal carotid. Occlusion at bifurcation.	Left common carotid arteriogram	Transient aphasia and right arm weakness two years. Marked expressive aphasia, eight days.	Marked	2 weeks	S2 left lateral; S3 prefrontal, left temporal, and parietal
3. J.M. 257211 61 M	Left internal carotid. Occlusion at bifurcation.	Left common carotid arteriogram	Thick speech, transient, two months. Episode expressive aphasia and right-sided weakness, arm more than leg, six weeks. Increasing aphasia, three weeks.	Marked	3 weeks	S3 left temporal
4. S.J. 245014 72 F	Right internal carotid. Occlusion at bifurcation.	Right common carotid arteriogram	Eight to ten hour onset of left hemiparesis, denial of left extremities, left homonymous hemianopia.	Marked	6 days	S3 prefrontal, left motor and temporal; VD-P right lateral
5. J.M. 175814 53 M	Right internal carotid. Occlusion of cervical segment. Ophthalmic artery collateral flow.	Right common carotid arteriogram	Transient right arm weakness, two years; postoperative (sympathectomy) sudden onset of left hemiparesis, left facial weakness, and left hemisensory deficit.	Marked	7 days	S3 right frontotemporal; S2 right parietal; S1 right lateral
				Marked	1 month	S3 right frontal and anterior temporal; VD right lateral
6. E.L. 164410 50 F	Left internal carotid. Ophthalmic artery anastomotic flow.	Left common carotid arteriogram	Transient weakness, right arm, one month. Right hemiparesis and expressive aphasia, two weeks.	Moderate	2 weeks	S3 focal left anterior temporal and intermittent prefrontal
				Mild	9 weeks	S1 left anterior temporal
				Mild	6 months	S2 intermittent left anterior temporal
				Mild	7 months	S1 left anterior temporal
7. R.S. 118521 42 F	Right internal carotid in siphon.	Right common carotid arteriogram	Intermittent left finger twitchings, eight months. Marked and persistent left-sided weakness, six months. Emotional lability, two months. Diminished visual acuity right eye.	Marked	6 months	S3 intermittent right anterior temporal; S2 right posterior temporal; Sp right temporal
8. J.C. 251621 64 M	Left internal carotid. Completely occluded in neck. Right internal carotid markedly narrowed in neck.	Post mortem	Eccentric behavior for many years. Increasing vertigo, drowsiness, disorderliness, and indifference, one to two months. Truncal ataxia, organic mental syndrome, mild right arm weakness, dysarthric, confused speech, and left optic atrophy.	Marked	5 weeks	S3 general with right temporal focal accentuation
9. J.L. 302923 50 M	Left internal carotid. Marked narrowing in neck and siphon.	Bilateral common carotid arteriogram	Diabetic, eighteen years. Numbness of right hand progressing to elbow, six months. Progressive, remittent nominal aphasia, three to four months. Intermittent right arm and leg weakness, three months.	Moderate	3 months	S3 left anterior temporal; S2 left frontal, posterior temporal, motor, and parietal
				Mild	7 months	S2 intermittent temporal
10. A.S. 144427 58 M	Left internal carotid. Occlusion at bifurcation. Flow via	Left common carotid arteriogram	Episodic, expressive aphasia, eighteen months. Clumsiness of right hand, fifteen months. Intermittent right leg	Moderate	3 months (first admission)	Normal
019085 (384427) 50 M	Occlusion just above bifurcation. Good flow via ophthalmic artey.	arteriogram	Episodic speech difficulty, seven days. Right arm and hand weakness and clumsiness, mild receptive aphasia, and dyscalculia.			

10.	A.S. 144427 55 M	Left internal carotid. Occlusion at bifurcation. Flow via	Left common carotid arteriogram	Episodic, expressive aphasia, eighteen months. Clumsiness of right hand, fifteen months. Increasing right leg	Moderate	3 months (first admission)	Normal
	019085 (384427) 50 M	Occlusion just above bifurcation. Good flow via ophthalmic artey.	arteriogram	Episodic speech difficulty, seven days. Right arm and hand weakness and clumsiness, mild receptive aphasia, and dyscalculia.			
12.	L.G. 284527 59 M	Right internal carotid. Occlusion at bifurcation. Retrograde flow via ophthalmic artery.	Right common carotid arteriogram	Irritability, intermittent disorientation, and confusion, five months. Left-sided weakness, two months. Accelerated advance of symptoms, ten days.	Extreme	10 days	S3 general with right-sided preponderance of abnormality
13.	M.L. 048430 71 F	Right internal carotid. Occlusion intracranial portion. Left internal carotid. Atheromatous changes in intracranial portion.	Post mortem	Left hemiparesis with recovery, four months. Fever of unknown origin on admission. Later increasing lethargy and left-sided weakness.	Extreme	3 weeks	S3 left posterior; VD right lateral
14.	J.O. 1311637 75 M	Right internal carotid. Occlusion at bifurcation.	Right common carotid arteriogram	Episode of weakness of left arm and face with slurred speech, one year. Progressive weakness left hand and arm, three weeks—becoming marked, one week.	Moderate	1 week	Normal
15.	J.M. 214938 48 M	Right internal carotid. Occlusion at bifurcation. Flow via ophthalmic artery.	Right common carotid arteriogram	Intermittent numbness, left hand, five weeks. Left hand weakness, four weeks. Episodic light headedness, three weeks.	Moderate	6 weeks	S3 right anterior temporal at low voltage
16.	S.K. 192641 56 M	Left internal carotid. Occlusion in siphon.	Left common carotid arteriogram	Intermittent blurred vision and numbness of right arm, three weeks. Brief episode of inability to speak, two weeks. Right-sided weakness and impaired speech, one week. Drowsiness and twitching of right face and tongue, two days.	Marked	1 week	S3 left frontal temporal and motor; S1 left lateral
					Marked	4 weeks	S3 left temporal; S2 left lateral
17.	N.G. 308849 41 M	Thrombosis of common carotid vessel graft, right.	Surgery	Resection carotid body tumor, right, and insertion of common carotid vessel graft. Sudden onset twelve days later of left arm and face—and, to lesser degree—left leg weakness.	Marked	5 days	S3 right anterior and posterior temporal; S3 transient, left parietal and motor; Sp slow, right anterior and posterior temporal
					Moderate	5 weeks	S3 right anterior and posterior temporal
18.	W.M. 983855 62 M	Left internal carotid. Occlusion at bifurcation. Large dilated ophthalmic artery with retrograde flow.	Left common carotid arteriogram	Sudden onset of right hemiparesis, right facial weakness, and mixed aphasia with initial unconsciousness.	Marked	3 days	S3 left posterior temporal; S1 lateral left
					Marked	2 weeks	S3 left posterior temporal; S1 bilateral
					Marked	1 month	S3 left posterior temporal; S1 general, left
19.	J.F. 201264 60 M	Right internal carotid. Complete block at level of angle of mandible. Retrograde flow via ophthalmic artery.	Right common carotid arteriogram	Stiffness of left hand and arm for two hours, ten days. Transient paresthesis left hand, two days. Sudden onset of left-sided weakness, two days after admission. Left arm, face and to less degree, leg weakness; mild expressive aphasia; left hemisensory deficit.	Moderate	1 day	S3 right posterior temporal and parietal; S2 right lateral
					Moderate	5 days	S3 right frontal and anterior temporal; S2 right lateral
					Moderate	3 weeks	S1 general
					Mild	2 years	S1 mild, right lateral
20.	J.M. 194067 52 M	Right internal carotid. Occlusion 1.5 cm. above bifurcation. Retrograde flow in ophthalmic artery.	Right common carotid arteriogram	Numbness, left hand, six months. Weakness of left hand grip, four to five months. In addition to moderate left hand and arm weakness, left-sided cortical sensory deficit, and left inferior quadrantanopsia noted.	Mild	4 months	Normal

TABLE 1—(continued)
CASE SUMMARIES: MAJOR CLINICAL AND ELECTROENCEPHALOGRAPHIC FINDINGS

Case Age, Sex	Site and nature of occlusion	Verification	Clinical features	Severity of neurologic deficit at time of EEG	Duration of most recent symptoms at time of EEG	EEG description (See text for definition of terms)
21. S.W. 097367 69 F	Left internal carotid. Occlusion just above bifurcation.	Bilateral common carotid arteriogram	Intermittent episodes of numbness of right side of face and tongue, and right arm lasting five to fifteen minutes, six months. Sudden onset of inability to speak on day of admission.	Marked	2 days	S3 lateral left, most prominent left frontotemporal; S2 paroxysm right anterior temporal; VD lateral left
22. R.R. 229767 60 M	Left internal carotid. Occlusion just above bifurcation. Retrograde flow via ophthalmic artery.	Left common carotid arteriogram	Dull, aching, tired feeling in right arm, two months. Incoordination right arm and weakness of right hand, one month. Unsteady gait, three weeks. After arteriography, developed marked right-sided weakness, expressive aphasia and cortical sensory abnormality referable to right arm.	Mild	1 month (before arteriogram)	Normal
				Moderate	18 months (after arteriogram)	S3 left temporal and intermittent left prefrontal
23. V.L. 296871 55 M	Left internal carotid. Occlusion at bifurcation. Collateral flow via large ophthalmic artery.	Left common carotid arteriogram	One- to two-second episodes of sleepiness, left arm, one year. Progressive weakness, left hand, six to twelve months. Clumsiness of left hand, one month. Progressive stiffness of left arm, three days.	Mild	1 week	Normal
24. N.M. 946473 46 M	Left internal carotid. Markedly narrowed intracranial portion. Right internal carotid dilated and filled with fresh thrombus.	Post mortem	Fifteen-second attack of unconsciousness followed by persistent right frontal headache, ten days. Weakness and numbness of right hand, two days. Largely expressive aphasia, right face and arm weakness, one day. Downhill course after ventriculography.	Marked	2 days	S3 left temporal; S1 left lateral
25. H.H. 103779 55 M	Left internal carotid. Occlusion at bifurcation.	Left common carotid arteriogram	Transient right hand weakness for one-half hour, six months. Two-week period of paralysis of right arm, five to six months. Onset of mild, expressive aphasia, facial asymmetry, and intermittent right arm weakness, two weeks.	Moderate	2 weeks	S3 left temporal; S1 left lateral
26. R.M. 092983 54 M	Right internal carotid. Occlusion at bifurcation.	Bilateral common carotid arteriogram	Persistent soreness of anterolateral aspect of left thigh and left leg weakness, eighteen months. Mild left leg weakness, left-sided reflex preponderance, and left Babinski on examination. Downhill course after subdural pneumoencephalogram.	Mild	18 months	S3 right anterior temporal and motor; S1 right lateral; Sp right anterior temporal
				Marked (after pneumoencephalogram)	1 day	S1 general; VD-P right lateral
27. E.B. 144486 50 M	Right internal carotid. Occlusion 1 cm. above bifurcation. Enlarged ophthalmic artery.	Bilateral common carotid arteriogram	Episode of left-sided paralysis, two years. Mild mental confusion, slowing, and irritability, two years. Left-sided weakness, hyperreflexia left [illegible] sias of right fingers, thirteen months. Numbness and weakness of right hand, two months. Transient weakness of right leg, paresthesias right side of face, one month.	Mild	2 years	VD right parietal and occipital, mild
	61 M	tion.				

50 M	bifurcation. Enlarged ophthalmic artery.		ing, and irritability, two years. Left-sided weakness, hyperreflexia left				
61 M	tion.		sias of right fingers, thirteen months. Numbness and weakness of right hand, two months. Transient weakness of right leg, paresthesias right side of face, one month.				
29. P.H. 118689 40 F	Right common carotid. Markedly delayed filling.	Angiocardiogram	Left handed. Thick speech, weakness of left arm and leg on awakening, five weeks. Exacerbation after improvement of left arm and leg weakness, two weeks. Left arm paralyzed, left leg weak, and left-sided cortical sensory deficit on examination.	Marked	7 weeks	S3 right anterior temporal; S1 general, mild	
30. D.A. 259886 48 M	Right internal carotid. Generally markedly narrowed throughout. Flow stops in siphon.	Bilateral common carotid arteriogram	Intermittent headache, right parietal, one year. Dizziness, left-sided weakness, one month. Marked increase in left-sided weakness and slurred speech, two days. Lethargy, paralysis of left arm, paresis of left leg, left homonymous hemianopia, left facial weakness, deviation of eyes to right and left hemisensory deficit on examination.	Marked Marked	7 days 18 months	S3 left anterior and posterior temporal; VD-P right lateral S3 bifrontal; VD-P right lateral	
31. F.H. 897191 73 F	Left internal carotid. Markedly narrowed in intracranial portion.	Left common carotid arteriogram	Increasing weakness of right arm and anomia, two weeks.	Mild	2 weeks	S3 left anterior and posterior temporal; S1 general, left	
32. I.P. 269092 43 F	Left internal carotid. Occlusion 1 cm. above bifurcation.	Left common carotid and left vertebral arteriograms	Episode of headache and thick speech, twenty-six months. Episode of right-sided weakness and inability to speak, twenty-five months. Onset of right-sided seizures, fifteen months. On examination, residual right hemiparesis most marked in arm.	Mild	2 years	S1 general with left lateral accentuation	
33. W.W. 177295 56 M	Right internal carotid. Occlusion at bifurcation.	Right common carotid arteriogram	One- to two-minute episodes of: inability to speak and weakness of left leg, three years. Numbness and weakness of left hand with associated cortical sensory deficit, two months. Occipital headache, one week.	Mild	2 months	S1 general	
34. K.J. 118798 63 M	Left internal carotid. Occlusion at bifurcation.	Left common carotid arteriogram	Three-week episode of numbness of right hand, speech difficulty and right homonymous field cut, ten months. Sudden onset right arm weakness and mild expressive aphasia, two days.	Moderate	11 days	VD left lateral	
35. E.W. 121296 64 M	Left internal carotid. Occlusion at bifurcation.	Left common carotid arteriogram	Progressive weakness of right hand preceded by transient numbness of right fourth and fifth fingers, six weeks.	Mild	2 months	Normal	

Fig. 1. I.P. (Case 32). Arrow points to occlusion of internal carotid artery 1 cm. above bifurcation of common carotid.

Fig. 2. M.G. (Case 1). Arrow points to stenosis of internal carotid artery just above the bifurcation of the common carotid.

its well-modulated 8 to 12 cycle per second activity in the posterior areas, low-voltage fast activity anteriorly, and no focal, lateral, or paroxysmal abnormalities. The appearance of activity at less than 8 cps part of the time is designated S1. S2 records are characterized by the appearance of intermittent 4 to 6 cps activity or less than 8 cps activity all the time. An S3 classification indicates the presence of waves of less than 4 cps at least part of the time. VD indicates a focal voltage depression. When voltage depression is profound and extends over most of or over an entire hemisphere, the symbol VD-P is used. The presence of spikes and clear-cut paroxysmal activity is recorded as Sp and Parox, respectively. The locations of focal abnormalities are designated.

CLINICAL OBSERVATIONS

Of the 35 patients, 26 were men and 9 women. Ages at the time of hospitalization ranged from 40 to 73 years. Average age was 56.

The left internal carotid artery was the site of the lesion in 20 patients, the right in 11. The vessels were completely occluded in 27 and markedly narrowed in 4 (Figs. 1 and 2). Lesions were found at or just above the bifurcation in 25 patients and in the carotid siphon or above in 5. Marked narrowing of the cervical and intracranial portions of the internal carotid artery occurred in 1.

More unusual lesions were found in the 4 remaining patients. In 2 who subsequently died, severe, bilateral internal carotid lesions occurred. In 1, Case 8, atherosclerotic occlusion in the cervical portion was complete on the left and almost complete on the right. The other, Case 24, more fully discussed below, had lesions in the intracranial portions of both carotids.

Another patient, Case 29, had thick speech and episodic weakness of the left extremities for six weeks. The right carotid pulse was absent; the right radial pulse was diminished. An angiocardiogram revealed delayed filling of the right common carotid artery. The fourth of the more unusual lesions was an extensive thrombosis in a right common carotid arterial graft implanted after excision of a carotid body tumor (Case 17).

Symptoms. Onset was episodic (stuttering) in 22 patients, slowly progressive in 10, and sudden and persistent in 3. In 18 patients, the initial symptom occurred in the upper extremities. The initial involvement of the upper extremity appeared as an isolated phenomenon

in 11 patients or in association with the following symptoms: aphasia in 2; numbness of the face and aphasia in 1; numbness of the face and tongue in 2; facial weakness and slurred speech in 1; and blurred vision in 1. Arm symptoms were variously described as: weakness in 9; sleepy, tired, or numb feeling in 7; stiffness of the arm and hand in 1; and twitching of the fingers in 1.

An aphasic onset was noted either as an isolated symptom or in combination with other symptoms in 8 of 23 patients with dominant hemisphere lesions. An initial hemiparesis was described by 4 patients. Another exhibited a hemiparesis following a period of unconsciousness.

Organic mental syndromes characterized by a variety of symptoms variously described as eccentric behavior, depression, irritability, difficulty concentrating, and confusion were the first symptoms in 3 patients.

The original symptom was described by 2 patients as a peculiar sensation in a leg. One noted paresthesias of the right thigh three months prior to the onset of paresthesias of the right hand; the other complained of a persistent soreness of the anterolateral aspect of the left leg.

The initial symptom was episodic lightheadedness in 1 patient. Headache was described as the first symptom by 1 patient and as a distressing symptom during the course of the disease by 2 other patients. Of these, 1 first noted headache after a brief period of unconsciousness.

Signs. Weakness of an extremity was present in all 35 patients. This varied from mild clumsiness of a hand to complete and profound flaccid paralysis. Arm weakness was present in 34 patients and was considered to be mild to moderate in 7 and marked in 27. Associated weakness of the ipsilateral leg was present in 23. In all but 1 patient, this impairment was considered to be of less degree than that in the arm and hand. The exception (Case 12) had been irritable and disoriented for five months and had had two months' progressive left-sided weakness. Examination revealed bilateral spastic weakness which was marked in the left arm and leg, moderate in the right leg, and mild in the right arm. A profound organic mental syndrome and varying degrees of lethargy were also noted.

The electroencephalogram (Fig. 3) was diffusely and markedly slow with right-sided preponderance of abnormality. Arteriography disclosed complete right internal carotid thrombosis in the neck. It was thought that the patient's unusual symptomatology could be accounted for by one of the following conditions: 1] an incomplete circle of Willis with both anterior cerebral arteries receiving their major blood supply from the affected artery, 2] partial occlusion of the other carotid artery, or 3]

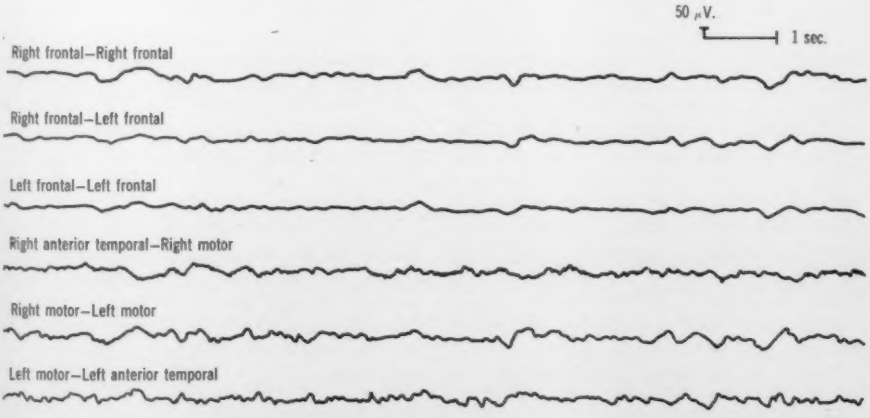

Fig. 3. L.G. (Case 12). The electroencephalogram shows marked generalized slowing (S3) with right-sided preponderance of abnormality.

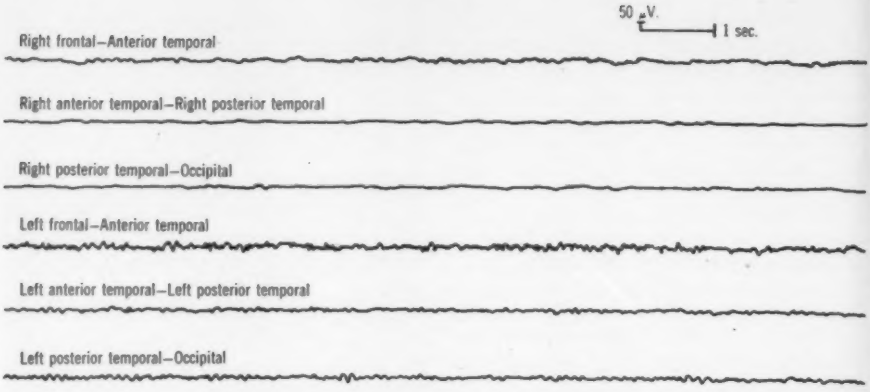

Fig. 4. R.M. (Case 26). One day after pneumoencephalogram a profound voltage depression is present on the right side.

a combination of both of these possibilities as was described in Clarke's well-documented case.[18]

Only 1 patient, Case 26, had weakness solely confined to the leg. Following a pneumoencephalogram, he developed a profound left hemiparesis and became oblivious of his left extremities. After the air study, a profound voltage depression appeared in the electroencephalogram (Fig. 4).

Of the 23 patients with dominant hemisphere lesions, 15 had varying degrees of aphasia which were largely expressive in 11, receptive in 1, and mixed in 3.

Astereognosis occurred in the affected hand of 11 patients; a hemihypesthesia, hemihypalgesia, or both in 10. Diminished position sense in the hand without stereognostic deficit was present in 4. Tactile inattention was specifically noted in 4 patients on the affected side.

Complete homonymous hemianopia occurred in 3 patients. A left inferior quadrantic hemianopia was present in 1. Diminished visual acuity in the eye ipsilateral to the carotid lesion was present in 2 patients. Funduscopic examination revealed optic atrophy in 1 of these. Deviation of the eyes to the side of the lesion was noted in 3 patients and was to the right side in each.

Severe organic mental syndromes occurred in 3. Marked lethargy at the time of admission was present in 4.

Diminished carotid pulsation was only noted in the 2 patients (Cases 17 and 29) who had disease of the common carotid artery. In this regard, it must be noted that during the period of collection of the present series of proven carotid occlusive disease, a number of patients had diminished carotid pulsations, ipsilateral ocular abnormalities, x-ray evidence of arterial calcification of the carotid, and other symptoms and signs felt to be characteristic of carotid thrombosis. The presence of these typical clinical signs obviated the need for arteriography, and, therefore, such cases are not included in this series.

Diastolic blood pressures of 100 or less were found in 31 patients. The diastolic pressure of the 4 remaining patients was 110 on admission. The highest recorded pressure was 210/110. A history of preexisting hypertension was rarely obtained. Of the patients, 2 were diabetic. Another exhibited a hypochromic anemia which was later found to be secondary to a carcinoma of the cecum. Only 1 patient was unusually obese.

A spinal fluid examination was performed on 26 of the patients. All pressures were within normal limits. Total protein ranged from 32 mg. per cent to 60 mg. per cent in 18 patients and from 60 mg. per cent to 90 mg. per cent in 7. The protein value in the remaining patient was 117 mg. per cent. No cerebrospinal fluid pleocytosis was recorded. A Westergren erythrocyte sedimentation test was performed on the blood of 21 patients.

A value below 20 mm. per hour was obtained in 17. Only 1 value, 43 mm. per hour, exceeded 30 mm. per hour. The mean erythrocyte sedimentation rate was 14 mm. per hour.

Clinical course. A discussion of therapy and the utlimate clinical course of these patients is beyond the scope of this report. This aspect of the problem of carotid occlusive disease is, however, reviewed in recent papers by Jackson and Fromm,[19] Meyer and associates,[20] Fisher,[21] and Sastrasin.[22] The response of the group, however, to the stress of special x-ray diagnostic procedures merits special attention.

Arteriography was attempted in 32 patients. During the procedure short of successful injection, 1 patient with bilateral disease developed generalized seizures. Twenty-seven unilateral and 4 bilateral studies were successfully performed. No change in clinical status was noted subsequent to the bilateral studies. Within two hours, 4 unilateral studies were followed by marked increase in focal deficit which persisted in 2 and largely cleared in 2, 1 of whom was treated with intermittent CO_2 inhalation; the other was treated with anticoagulants. No deaths occurred in this group. Sequellae of the air studies proved more severe.

Ventriculography was performed on 2 patients—Case 24 as the sole special diagnostic procedure and Case 8, following an unsuccessful attempt to perform an arteriogram. On the day after a normal ventriculogram, Case 24 had increasing aphasia and right-sided weakness. Persistent generalized seizures appeared ten days later followed by coma and death. At autopsy, atheromatous changes in the intracranial portion of the left internal carotid artery were noted. These changes markedly compromised the caliber of the vessel. The right internal carotid artery also demonstrated atheromatous changes but, unlike its opposite, was quite dilated intracranially. A fresh, gray-red thrombus lay at the junction of this vessel with the right middle cerebral artery. Atheromatous changes were present also in the first 2 cm. of the right middle cerebral artery. Section of this vessel also revealed fresh thrombus proximally. Significantly, no remarkable abnormalities were noted in the branches of the left internal carotid artery. In the cerebrum were 2 series of lesions. On the left, scattered infarcts, considered to be a number of weeks old, were noted in the parietal cortex —chiefly in the supramarginal area and also in the subcortical white matter of the posterior portion of the frontal and parietal lobes. On the right, a large area of fresh encephalomalacia occupied the major portion of the caudate nucleus, internal capsule, lenticular nucleus, island of Reil, superior temporal gyrus, and hippocampus.

On the day following ventriculography, Case 8 became stuporous and suffered increasing respiratory difficulty; death occurred three days later. The ventriculogram revealed diffuse cortical atrophy.

Prior to arteriography, 4 pneumoencephalograms were done; 2 patients suffered no untoward effects. In both, the studies were unremarkable. The other 2 patients, however, had a marked increase in the degree of focal impairment after the procedure. Prior to pneumoencephalography, case 25 exhibited a mild right-sided weakness and mild expressive aphasia. The pneumoencephalogram was nonfilling. Shortly after the procedure, the patient had a convulsion. The seizure began in the right hand and became generalized. Postictally, a profound and persistent right hemiparesis appeared. After arteriography—which demonstrated complete obstruction of the left internal carotid at the bifurcation—the patient was administered anticoagulants. No improvement occurred. On the day following a subdural air injection, the other patient, Case 26, suddenly became oblivious of his left extremities and developed a profound left hemiparesis. Subsequently, arteriography revealed thrombosis of the right internal carotid artery at the bifurcation. The patient died shortly, after a craniotomy done because of the persistent suspicion of brain tumor.

These ill effects of air studies in 4 of 6 patients argue strongly against the employment of air studies in cases where differential diagnosis includes carotid occlusive disease. Similar experience with air studies in this disease has been reported by Solomon and Baron.[23]

ELECTROENCEPHALOGRAPHIC STUDIES

Normal electroencephalograms were exhibited in 8 patients either initially or at some

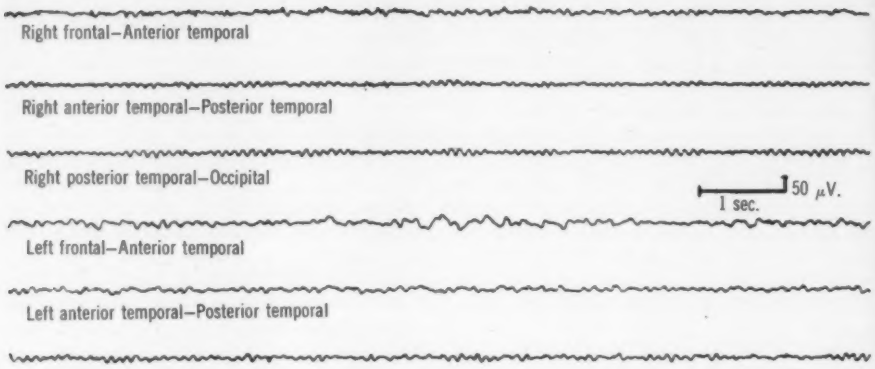

Fig. 5. R.R. (Case 22). A persistent focal slowing in the left frontotemporal area is present eighteen months after acute aggravation of symptoms following arteriography.

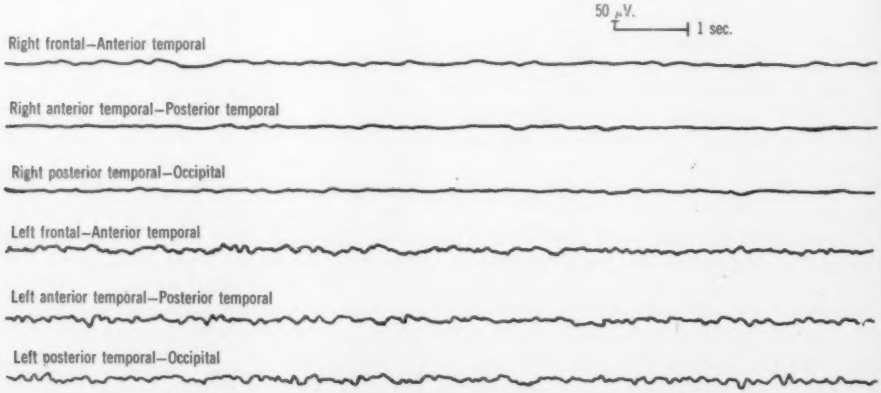

Fig. 6. M.L. (Case 13). The record shows a marked voltage depression (VDP) on the right and marked left-sided slow wave (S3) abnormality.

point in the course of the disease. In this group, Case 22 had mild right arm weakness. At admission, electrical study was normal. After arteriography, however, he developed marked right-sided weakness, expressive aphasia, and a cortical sensory deficit referable to the right arm. A persistent S3 focal abnormality was recorded eighteen months after this episode (Fig. 5). Another patient, Case 15, two and one-half years prior to a normal recording, exhibited a slow-wave S3 focus six weeks after onset of symptoms. In all, only 9 of 52 records were normal. The remaining 43 records revealed a wide variety of abnormalities. In several patients, more than one kind of abnormality was present. For this reason, a brief summary of all cases is presented in Table 1.

Abnormal electroencephalograms occurred in 29 patients some time during their illness; 20 had clearly focal, severe S3 slow-wave abnormalities in an area appropriate to the clinical findings. A voltage depression—generally over the involved hemisphere—was also observed in 3 of these patients.

Records of 3 other patients revealed a

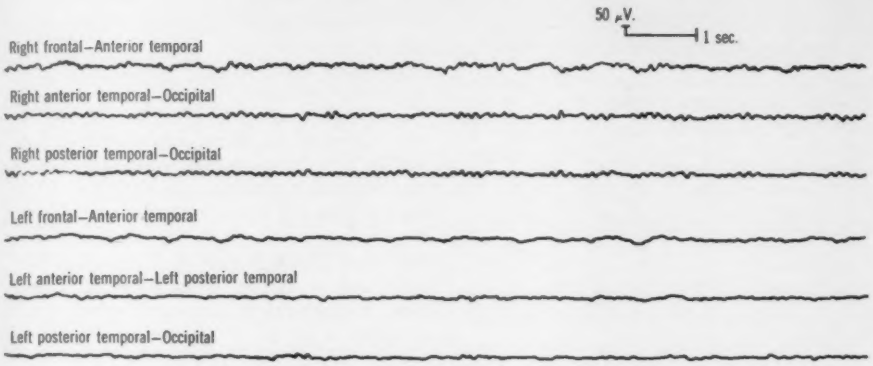

Fig. 7. K.J. (Case 34). Voltage depression (VD) on the left side is the only abnormality seen on record taken eleven days after onset of most recent symptoms.

marked slow-wave abnormality ipsilateral to the focal clinical signs and a profound voltage depression over the cortical regions appropriate to the symptoms. This voltage depression persisted for a period of eighteen months in 1 patient, Case 30, after the most recent change in symptoms. Another patient, Case 13, had a history of left hemiparesis with subsequent clearing four months prior to her admission for unexplained fever. During her hospitalization, the fever subsided but the patient manifested increasing drowsiness and clumsiness of the left arm progressing to left-sided weakness. The electroencephalogram revealed marked voltage depression, VD-P, on the right and marked left posterior temporal S3 slow-wave abnormality (Fig. 6).

The increasing drowsiness, the appearance of mild dilation of the left pupil, and the voltage depression contralateral to the focal signs suggested the diagnosis of subdural hematoma. Trephination, however, was negative. Clinical course was progressively downhill, and the patient died in the sixth week of hospitalization. Autopsy revealed a heavy atheromatous plaque in the wall of the right internal carotid artery which reduced the lumen to one-half normal size and a 3 to 4 mm. firm thrombus in the distal portion of the artery. Only mild atheromatous changes were noted in the opposite internal carotid artery. No other remarkable alterations occurred in the intracranial arteries. Section of the brain disclosed multiple patchy areas of old encephalomalacia in the right superior parietal, right supramarginal, right angular, and right middle and superior frontal gyri. Fresh encephalomalacia was also observed in the above areas and in the posterior three-fifths of the right temporal lobe, over the medial face of the right occipital lobe, and more deeply in the right island of Reil, right extreme and external capsules, right claustrum, and lateral margin of the right putamen.

Marked generalized slowing, S3 general, appeared in the records of 2 patients. Clinically, both exhibited bilateral signs and marked organic mental syndromes (Fig. 3). Mild generalized slowing, S1 general, was noted in the records of 2 others. A focal voltage depression, VD, alone was observed in 2 cases; in both, the depression was localizing (Fig. 7).

In 4 patients with seizures attributed at least in part to their vascular lesions, paroxysmal activity did not occur. Only 1 of these patients (Case 32) actually had had focal seizures. These began one year after the onset of right-sided weakness and mild expressive aphasia. As noted above, the other 3 had convulsions only in conjunction with or following special x-ray procedures.

On the other hand, electroencephalograms showed focal paroxysmal abnormalities in 3 patients without seizures (Table 1).

Intermittent twitching of involved areas was described by 2 patients. Their records, however, failed to reveal seizure activity.

Of particular interest was the relation of the

TABLE 2

RELATION OF EEG FINDINGS TO DURATION OF MOST RECENT SYMPTOMS*

Duration, most recent symptoms	*Normal record*	*VD*	*S1*	*S2*	*S3*	*Sp*
0 to 1 week	1	4	5	3	10	1
1 to 2 weeks	0	1	2	2	7	0
2 to 4 weeks	2	2	2	1	5	0
1 to 3 months	2	0	3	1	7	0
3 to 6 months	1	0	0	2	1	0
6 to 12 months	0	0	1	1	0	0
12 to 18 months	1	1	1	0	3	1
18 to 30 months	1	1	2	0	0	0

*Where more than 1 abnormality occurs in a single record, each is listed separately.

electroencephalographic findings to the duration of the most recent symptomatology. The relationship is detailed in Table 2.

Cerebral changes induced by carotid occlusive disease cause changes in the electroencephalogram which, in many patients, persist far beyond two weeks. While a tendency exists in some patients for the tracing to revert toward electrical normality, persistent marked abnormailties were noted for periods of two weeks to eighteen months in 15 patients (Figs. 5, 8, and 9). Again, if all recordings were dated from the time of onset of the original symptom, a far greater proportion would ex-

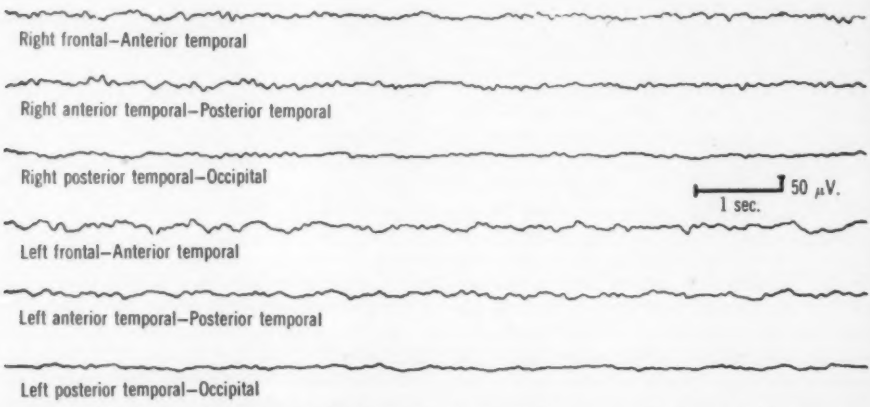

Fig. 8. J.L. (Case 9). Three months after onset of symptoms a persistent slowing (S2) occurs on left side, most marked (S3) in the left anterior temporal area.

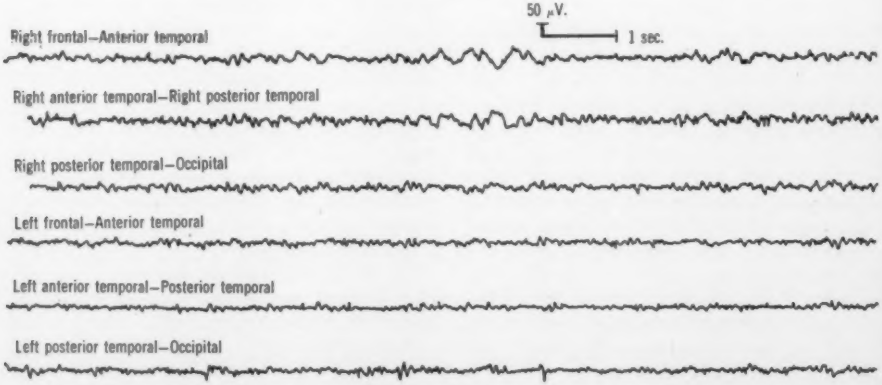

Fig. 9. R.S. (Case 7). Persistent, intermittent slow wave (S3) focus in right anterior temporal area six months after onset of symptoms.

hibit marked electrical changes long after the onset of illness.

Abnormalities in the electroencephalogram in carotid occlusive disease may not only persist but become progressively worse with time, simulating serial records seen in patients with brain tumor. Case 18 suffered a sudden and dramatic onset of unconsciousness while sitting on a park bench. Shortly thereafter, he was alert on admission. A mixed aphasia, more expressive than receptive, was present. The right arm was flaccid and useless. The right leg was quite weak distally. A mild right central facial weakness and right hemihypesthesia were also noted.

Electroencephalograms were made on the third, fourteenth, and thirtieth hospital days. All revealed a marked slow-wave focus in the left posterior temporal area and mild generalized left-sided slowing (Fig. 10). The abnormalities on the fourteenth day appeared worse than those on the third day, and the record was only mildly improved after one month. During this period, the patient's skull

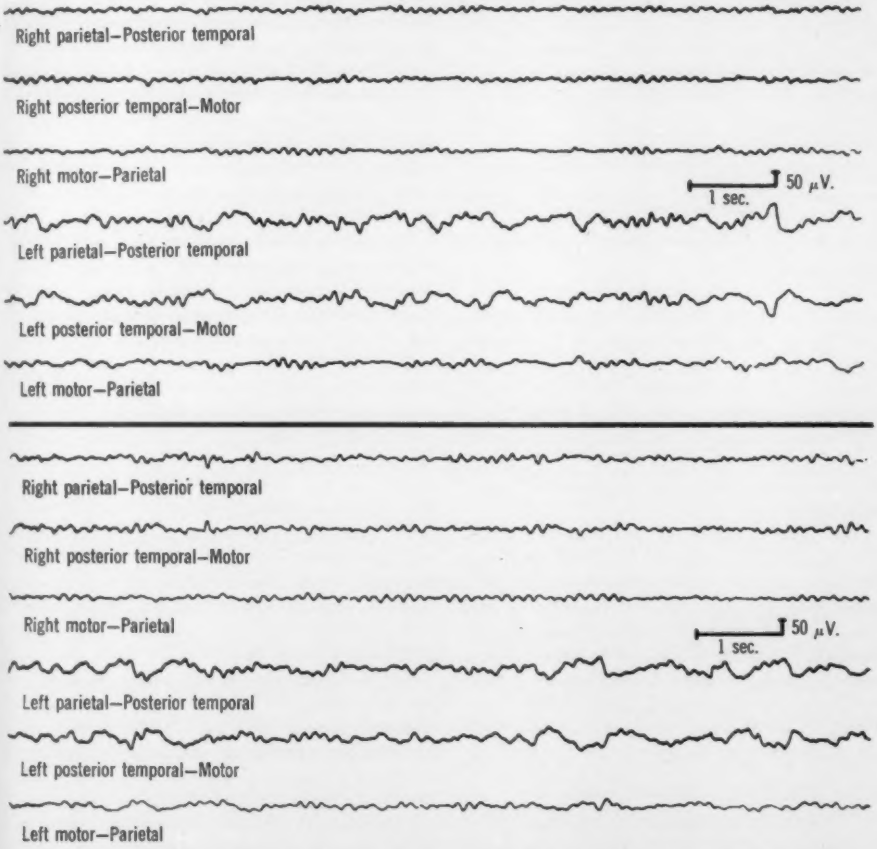

Fig. 10. W.M. (Case 18). *(Top)* Marked slow wave focus (S3) in the left posterior temporal area on the third day after the appearance of symptoms. *(Bottom)* Marked slow wave focus (S3) in left posterior temporal area fourteen days after onset of symptoms. Mild slowing (S1) now extends to the right side.

TABLE 3
RELATION OF ELECTRICAL ABNORMALITY TO SEVERITY OF NEUROLOGICAL DEFICIT

Neurologic deficit	*Normal record*	*Markedly abnormal record*
Mild	4	2
Moderate	4	8
Marked	0	19
Extreme	0	3

x-rays exhibited progressive migration of the pineal body to a point 5 mm. to the right of the midline. Although the patient's clinical status during this period was, if anything, slightly improved, the serial electrical and x-ray studies prompted the performance of a left-carotid arteriogram one month after admission to rule out the possibility of brain tumor. A complete thromobsis of the internal carotid was found at the bifurcation. A huge ophthalmic artery was also demonstrated. Through this vessel, dye entered a midline anterior cerebral artery. After the procedure, the patient's clinical status gradually improved.

In order to compare the degree of neurologic deficit with the electroencephalographic changes, the severity of neurologic impairment was graded at the time of each electroencephalogram. Our classification, while admittedly rough and arbitrary, does yield some useful information when the incidence of normal or markedly abnormal (S3 and VD-P) records is compared for each of the 4 grades of neurologic deficit (Table 3).

The table confirms the impression of Jones and Bagchi[10] and reveals a general tendency for the degree of electroencephalographic abnormality to parallel the severity of the symptoms. Profound electroencephalographic changes, however, may occur in some patients with minimal or moderate degrees of impairment. On the other hand, when marked neurologic changes are present, marked electrical abnormalities may be expected.

EFFECTS OF POSTURAL TILTING

The authors collaborated with Dr. Elliott Weitzman to study the effects of postural tilting on the electroencephalographic records of 7 of the patients in this group. At the time of the postural tilting, none had exhibited recent fluctuation of symptoms. The studies were done from one month to two years after the most recent exacerbation of symptoms. In this respect, the patients differed from those studied by Meyer and associates[24] whose symptoms at the time of study were more fleeting.

A normal resting record was exhibited by 1 of the patients. Mild focal slowing was present in the pretilt records of 2. Prior to tilting, a marked slow wave focus was noted in the other 4 records. Except for some mild, further slowing in 1 of the markedly abnormal records, postural tilt produced no new changes—nor were the well-established changes intensified by tilting to 80° for periods of up to five minutes. However, no cases so examined exhibited the marked drop in mean systemic blood pressure noted by Meyer and associates.[24]

COMMENT

It is difficult to compare groups of patients more persistent and severe neurologic deficits. whose common disease exhibits signs and symptoms as protean as those observed in carotid arterial disease. Even in a consecutive series, selection occurs before the patients reach the hospital. The process tends to weed out patients with mild and transient symptoms and to select a disproportionate number with

In the hospital, the process continues to remove those with obvious syndromes—further modifying the character of the group which eventually satisfies the formal criteria for inclusion in the series. Indeed, as a result of the factors described, many of the reported cases qualified for inclusion only because the ambiguous character of their disease, in part compounded by the electroencephalographic findings, required complete x-ray studies. The series, therefore, was weighted with diagnostic problems.

Our material, however, demonstrates a number of valuable clinical diagnostic features which appear in patients with unilateral carotid disease. These may be listed as follows: [1] Marked preponderance in men; [2] onset largely in the fourth to sixth decades; [3] frequent episodic or stuttering progression of symptoms—the syndrome of cerebral intermittent claudication described by Hunt;[25] [4] a marked tendency for the contralateral upper extremity to be the site of the initial motor or

sensory symptoms and of the most profound motor deficit on examination; [5] infrequent involvement of the optic radiations; [6] infrequent complaint of headache; [7] infrequent appearance of seizures either initially or as a sequel to infarction; [8] infrequent presence of high blood pressure; [9] persistence of palpable carotid pulses in almost all patients; and [10] normal cerebrospinal fluid and erythrocyte sedimentation rate values as a rule.

Electroencephalographic studies of this population are by comparison less specific. The large proportion of persistently abnormal records makes it probable that a degree of cerebral infarction was present in a large number of the patients reported. No single electrical abnormality emerged which appeared to be peculiar to cerebral dysfunction secondary to carotid occlusive disease. The abnormal patterns (S3 focal, S3 diffuse, and VD-P) which were present in most of our records were not distinguishable from those of intracerebral space-occupying lesions. The slow-wave abnormality did not always lateralize the lesion. The abnormality was contralateral to the side of the carotid occlusion in 3 patients and, instead, a profound voltage depression proved to be the lateralizing feature. Again, contrary to the commonly accepted notion of rapid resolution of electroencephalographic abnormalities with time, the patients reported here often exhibited severe and persistent electrical abnormalities.

SUMMARY

A consecutive series of 35 patients with verified carotid occlusive disease is reported. All patients were studied electroencephalographically.

The electroencephalographic abnormalities were mainly of the focal slow-wave variety, such as is often encountered in brain tumor. Some patients showed focal depression of voltage only. The degree of electroencephalographic abnormality generally paralleled the severity of neurologic deficit. The frequency of occurrence of electroencephalographic abnormalities in carotid occlusive disease was 83%, not significantly different from that of brain tumor. Persistent, severe abnormalities often last from months to more than a year, especially where neurologic deficit is marked.

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Aneurysms of the vertebral artery

Report of 5 cases

George Paulson, M.D., Blaine S. Nashold, Jr., M.D., and George Margolis, M.D.

ANEURYSMS OF THE VERTEBRAL artery which produce neurologic signs and symptoms are uncommon, yet the incidence in postmortem studies varies from 1 to 15% of all cerebral aneurysms.[1] Yaskin and Alpers[2] reviewed 67 cases in 1944, and since then less than 20 more have been reported. Several large series of vertebral arteriograms have demonstrated few aneurysms in this location.[3]

This is a report of 5 persons with vertebral aneurysms. In 1 case, a small aneurysm was found incidentally at postmortem examination. In the 4 other cases, a vertebral aneurysm was suspected; in 2 instances, vertebral arteriograms proved the diagnosis.

Surgery was performed in 3 cases. In 2, the aneurysms were identified and clipped. In the third, a syrinx of the cervical cord was aspirated, although the aneurysm was not identified until postmortem examination.

CASE REPORTS

Case 1 (J.F.): This 62-year-old man complained of a sudden dull right occipital headache and two days later lost consciousness for one hour. He was hospitalized, and a lumbar puncture revealed bloody cerebrospinal fluid which cleared in several days. Following this, he complained of double vision which disappeared after four months. The occipital headaches continued, but four years later they became sharper and more persistent and were associated with pain in the neck. The pain in the occiput was increased by coughing, rotating his head, or lying flat. The pain awakened him at night. Pressure on the left side of the neck increased the pain, while turning the head to the right relieved the pain. Five years after the onset of his headaches, he experienced a transient feeling as if he were "floating away" and, at this time, swallowing difficulty and numbness of the right arm and side were noted. These symptoms recurred twice in the next three days and then disappeared.

Eight months later, he noted numbness of the fourth and fifth fingers of the left hand and the fourth and fifth toes of the right foot. The right arm and leg became weak, and he was bedridden. The occipital and neck pain was so severe that he refused to move his head. He was nauseated and vomited. Double vision returned, and breathing and swallowing became difficult.

Physical examination. The patient's temperature was 36° C.; pulse, 100; respiration, 30 and shallow; and blood pressure, 150/100. He was a thin, emaciated man who spoke in a whisper and was dyspneic and cyanotic on minimal exertion. There was muscular spasm and extreme tenderness over the left side of the neck. Pain radiated into the right occiput on pressure over this region of the neck. His heart and lungs were normal.

Neurologic examination. The patient was oriented and cooperative. The right optic disk was blurred. Horizontal nystagmus was found on right and left lateral gaze. The right lower half of his face was weak, and the right half of the palate sagged. The gag reflex was hypoactive. Deep tendon reflexes in the right arm were hyperactive, and there was a hyperactive jaw jerk and a right extensor plantar response. He could move his right leg but not the right arm, and the muscles on that side were atrophic. The right intercostal muscles were paralyzed below the fourth rib. Appreciation of pinprick was absent on the left half of the neck. There was an ill-defined decreased appreciation of pinprick elsewhere on the left half of the body, while the right side was normal.

Laboratory data. Examinations of the blood and urine were normal. Serologic tests for syphilis were negative. The electroencephalogram was normal. Roentgenograms of the chest revealed a tortuous aorta. On skull roentgenograms, the pineal body was slightly shifted to the right but was still within normal limits. The cerebrospinal fluid was xanthochromic, with a protein content of 98 mg. per cent. A cervical myelogram revealed a partial obstruction at the region of C4 and C7. A lesion of the cervical cord was suspected, although a diagnosis of vertebral aneurysm was considered.

Operation. A cervical laminectomy was done; the spinal cord was swollen at the C4 level.

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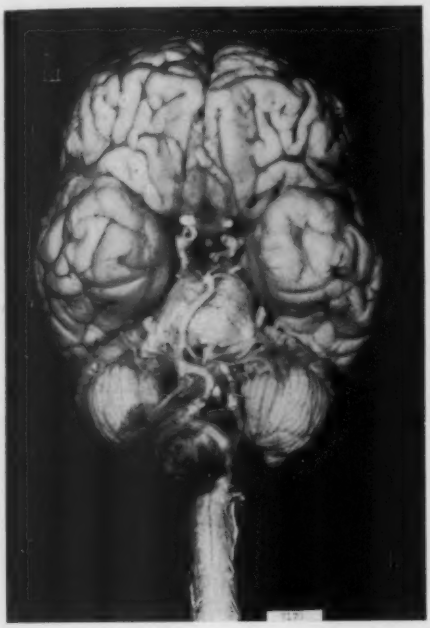

Fig. 1. Ventral view of brain and aneurysm in Case 1

Fig. 2. Compression of brain stem seen after removal of aneurysm in Case 2

Four cubic centimeters of turbid fluid was aspirated from a cavity in the cervical cord. The patient was given x-ray therapy postoperatively. Episodic nausea and vomiting followed surgery. Progressive respiratory insufficiency with frequent cyanosis occurred despite tracheotomy and suction. His respirations became irregular, and he died three weeks after surgery and six years after his first symptoms.

Pathologic anatomy. At autopsy, there was generalized arteriosclerosis with calcified plaques in the aorta and arteriosclerotic scarring of the kidneys. Arteriosclerotic aneurysms were present in both common iliac arteries. The coronary vessels were normal, and the heart was not enlarged. The circle of Willis was normal. There were moderate arteriosclerotic changes in the right vertebral artery. A saccular aneurysm, 4 cm. in diameter and with a 1.5-cm. neck, was attached to the left vertebral artery (Figs. 1 and 2). The aneurysm had flattened the lower portion of the medulla and collapsed the fourth ventricle. The cranial nerves in the posterior fossa on the right were stretched over the aneurysm. The cervical cord was distorted and soft, and there was old hemorrhage at the base of the brain. The cerebral cortex showed no gross changes. A thin-walled pouch on the surface of the aneurysm was thought to be the point of rupture. The lumen of the left vertebral artery was patent but narrowed by an old laminated clot. The aneurysm impinged on the origin of the anterior spinal artery.

Microscopic examination. The intima of the artery contained calcium deposits with some hemorrhage into the media, and there were a few focal areas of inflammatory infiltrate. The elastic lamina was fragmented near the aneurysm and absent in its wall. The thinnest area of the aneurysm contained only fibrous tissue without muscle or elastica. Sections of the lower medulla revealed a large central hemorrhage with extensive perihemorrhagic necrosis in the surrounding parenchyma. Multiple hemorrhages had occurred in the gray matter of the cervical spinal cord, involving the central canal, 1 lateral funiculus, and the apexes of the posterior columns. Focal areas of degeneration were present in the corticospinal tract and in the vestibulospinal areas. Above these regions, 1 lateral funiculus showed degenerative changes. Purkinje and granular cells were depleted in a few areas in the cerebellar folia.

Case 2 (A.M.): This 53-year-old man fell and struck the back of his head, without loss of consciousness, and developed occipital headaches. Within two years, the headaches had become severe and more frequent. His legs became weak, and he developed a staggering gait and com-

plained of dizziness, vertigo, and tinnitus. The headache was dull and steady in character and located in the occipital and suboccipital regions with radiation into the temporal areas of the skull. The severity of the headache was increased by sudden rotation of the head. It also was increased after eating a heavy meal or drinking alcohol.

Physical examination. Blood pressure was 180/110 supine but fell to 90/80 on standing. Pulse was 84; temperature, 37° C.; and respiration, 20. The patient was an obese man, alert and oriented. A soft systolic murmur was heard at the aortic area on the chest. Pain was produced by pressing over the suboccipital area and by moving the neck.

Neurologic examination. Funduscopic examination revealed tortuous retinal vessels. There was horizontal nystagmus, more pronounced on left lateral gaze. Fine vertical nystagmus was observed when the patient was standing but disappeared in the supine position. He fell backward and to the left side on Romberg test. There was a fine tremor of the outstretched hands. Sensation, motor power, and reflexes were normal.

Laboratory data. Blood and urine examinations were normal. Serologic tests for syphilis were negative. Value for blood cholesterol was 112 mg. per cent. Electrocardiogram revealed a left axis deviation. A generalized cerebral dysrhythmia was noted on the electroencephalogram. Cerebrospinal fluid was xanthochromic, and the initial pressure was 270 mm. The fluid contained 276 crenated red cells, 6 lymphocytes, and 2 polymorphonuclear cells. Benzidine test on the cerebrospinal fluid was strongly positive, and the protein content was 220 mg. per cent. Three days later, the cerebrospinal fluid was still xanthochromic and the protein content was 110 mg. per cent. Roentgenograms of the abdomen, chest, and skull were normal, except for a tortuous calcified aorta.

A pneumoencephalogram showed symmetrically dilated ventricles and generalized cortical atrophy. The basal cisterns were enlarged. Bilateral carotid angiograms were normal, but a right vertebral angiogram revealed a bilobular enlargement of the artery just inside the foramen magnum. This was interpreted as an aneurysm of the right vertebral artery.

Operation. A right suboccipital craniotomy was performed, and an aneurysm of the right vertebral artery was found. The proximal branches leading into the aneurysm were clipped, but the aneurysm could not be mobilized. Because of the large size of the aneurysm, it was opened and a clot removed, resulting in a decrease in the size of the aneurysm. Following the surgical procedure, the patient's blood pressure dropped and breathing ceased. Positive pressure breathing was begun, and noradrenalin was given. The condition of the patient did not improve, and he died two days after surgery. The total duration of his symptoms was two years.

Pathologic anatomy. The heart weighed 525 gm. The systemic vessels and circle of Willis were moderately arteriosclerotic. The posterior communicating artery on the right was large, but the basilar artery was hypoplastic. On the right vertebral artery 4 mm. proximal to the basilar artery was a globular aneurysm measuring 4 cm. in diameter (Fig. 3). The wall of the aneurysm contained no elastica, and the lumen was almost obliterated by an organizing thrombus. Areas of calcification, round cell infiltration, and hemorrhage distorted the thin wall of the aneurysm. A surgical rupture near a small outpouching on the wall of the aneurysm was closed by 3 clips. A fresh extradural blood clot surrounded the medulla and upper spinal cord. An intramedullary hemorrhage extended from the medulla to the cervical cord. The cord also contained focal hemorrhages and swollen areas. The right hypoglossal and olivary nuclei were partially destroyed by hemorrhages. Both sixth nerves were markedly flattened beneath the aneurysm. The roots of the ninth, tenth, eleventh, and twelfth cranial nerves on the right were stretched over the aneurysm. Focal hemorrhagic areas were observed in the cerebellum, but the cerebral structures were normal.

Case 3 (R.M.): A 61-year-old mill worker developed sudden episodic weakness of both legs which caused him to fall. Three years later, he stopped work because of staggering; a year after this, he noted tinnitus and loss of hearing in the left ear. A year later, the left side of his face became weak. Seven years after the initial symptoms, he was admitted to a hospital with a complaint of left sided headache, nausea, and vomiting. Roentgenograms of the skull were normal, as was a pneumoencephalogram. The cerebrospinal fluid was xanthochromic with a protein content of 200 mg. per cent. He was discharged without treatment and was readmitted several months later to our care.

Physical examination. Blood pressure was 170/140; temperature, 98.6° F.; pulse, 88; and respiration, 22. Pressure over the cervical spine caused pain, and forward flexion of the neck produced left occipital and nuchal pain. He held his head tilted to the right side.

Neurologic examination. The patient's behavior was childish, and he had a poor memory for recent events. He walked with a wide-based, staggering gait. The Romberg test produced falling to the left side. The left corneal reflex was decreased. The left external rectus muscle was weak, and there was a coarse horizontal nystagmus on conjugate gaze. The left half of the face was weak, and he was deaf in the left ear, with a decrease in hearing in the right ear. The Weber test lateralized to the right ear. There was a normal caloric response on the right but none on the left. The gag reflex was absent. Deep tendon reflexes were normal, but an extensor plantar response was present on the right side. There was a mild dysmetria of the left arm but no decrease in muscle strength. Sensory examination was normal.

Laboratory data. Examination of the blood and urine was normal. Serologic test for syphilis was

Fig. 3. Aneurysm in Case 2 reflected to the right

negative. The value for the fasting blood sugar was 113; blood urea nitrogen, 12.5; and cholesterol, 280 mg. per cent. The phenolsulfonphthalein test for renal function and Regitine test for pheochromocytoma were negative. Electrocardiogram was normal.

Roentgenograms of the chest revealed calcific densities in the pleura along the right lateral wall of the chest. Skull roentgenograms showed an area of radiolucency with a surrounding area of sclerosis in the left parietal bone. The apexes and auditory meatuses of the petrous bones were normal on the Stenvers projection. Pneumoencephalogram was considered normal except for an increased amount of air over the surface of the brain. Symmetric bilateral slowing and voltage asymmetries in the frontal region appeared in the electroencephalogram. The cerebrospinal fluid was faintly xanthochromic with an initial pressure of 180 mm. and no cells. The cerebrospinal fluid protein content was 67 mg. per cent. Wassermann test for syphilis and colloidal gold test were negative. Twelve days later, the cerebrospinal fluid was still xanthochromic and the protein was 71 mg. per cent.

During this hospitalization, the patient had episodes of occipital headache associated with confusion, vomiting, and elevation of blood pressure to 240 systolic and 140 diastolic. He was discharged unimproved.

Second admission. Two weeks after discharge, he was readmitted because of constant headaches, generalized weakness, and vomiting. His speech was slurred, and swallowing was difficult. He was dehydrated, and rhonchi were heard throughout the lungs. Neurologic examination revealed severe dysarthria. The left half of the face was now paralyzed. Appreciation of pinprick was decreased on the left half of the face, and the corneal reflex was absent. The extremities on the left were flaccid, and there were bilateral extensor responses on plantar stimulation. At this time, the initial cerebrospinal fluid pressure was 148 mm. The fluid was slightly yellow, with a protein content of 71 mg. per cent. The patient had difficulty breathing and swallowing, and a tracheotomy was performed. A serum potassium value of 2.1 mEq. per liter was restored to normal levels without clinical improvement.

Operation. The left cerebellopontine angle was explored using local anesthesia. A large pulsatile mass completely filled this region, with elevation of the left lobe of the cerebellum. The wall of the aneurysm contained arteriosclerotic plaques, as did the left vertebral artery. The artery was clipped proximal to the aneurysm without reducing its

pulsation or size. The blood pressure, respiration, and electrocardiogram were not altered as a result of the occlusion. The patient was unimproved after surgery and died twenty-four hours later. An autopsy was not obtained.

Case 4 (G.P.): This 40-year-old man was discharged from the Army at age 25 because of severe hypertension. At this time, his blood pressure was 220/140, labile and uncontrolled with drugs. He complained of occipital headache, dizziness, and blurred vision. Three years later, a bilateral thoracolumbar sympathectomy was done with relief of symptoms, but the blood pressure remained elevated. At age 32, he developed frequent severe headache in the parietooccipital region. He had sudden episodes of nausea and vomiting associated with numbness of his fingertips. At this time, he was given digitalis for mild congestive heart failure. At 35, he suddenly had a severe headache and developed paralysis of his right side without loss of consciousness. A year later, examination revealed spastic hemiplegia. He was depressed and cried easily and still had episodes of dizziness, perspiration, blurred vision, and occasional vomiting. He was readmitted to the hospital three years later (age 38) because of severe headaches radiating from the left mastoid region into the back of the neck. Tinnitus and vertigo were present. The right hemiplegia was unchanged, and, in addition, an area between the left knee and ankle had decreased appreciation for pain and temperature. The palate sagged on the right, and the right half of the face was weak. Eighteen months later, he was readmitted because of loss of memory and severe emotional lability. He was ataxic and had blurred vision. The headache was now constant in the occipital region.

Physical examination. Blood pressure was 170/130; temperature, 98.6° F.; pulse, 80; respiration, 22. There was arteriovenous nicking of the retinal vessels but no hemorrhages or exudates. The patient's face was florid. He cried without provocation and became more flushed at these times.

Neurologic examination. He was disoriented. His memory for recent and past events was poor, and he was unable to do simple mathematics. Horizontal nystagmus was observed on conjugate gaze to the left, and there was vertical nystagmus. The left lateral rectus muscle was weak. There was slight ptosis of the right eyelid and slight weakness of the lower half of the right side of the face. His palate drooped on the right, and dysarthria was present. The right arm and leg were weak. Pain and temperature were decreased on the left side of the face and the lower portion of the leg. The reflexes were hyperactive bilaterally, especially on the right, with bilateral ankle clonus and bilateral Babinski signs. The snout and jaw reflexes were present.

Laboratory data. Blood and urine examinations were normal. Serologic test for syphilis was negative. Serum cholesterol was 225 mg. per cent. Electrocardiogram demonstrated left ventricular strain and hypertrophy. Slow waves predominated over the left hemisphere on the electroencephalogram. Skull roentgenograms were normal, and chest roentgenogram revealed slight cardiac hypertrophy. Cerebrospinal fluid had an initial pressure of 260 mm. The fluid was slightly xanthochromic, and no cells were seen. The total protein content was 60 mg. per cent.

Pneumoencephalograms showed a mass anterior to the pons pushing it backward and partially obstructing the aqueduct of Sylvius. Bilateral carotid arteriograms were normal. A left vertebral arteriogram revealed a dilated tortuous vessel displaced to the left and slightly across the midline. There appeared to be no basilar artery but only a high fusion of the vertebrals with a bulbous termination. Initial interpretation of the arteriograms proved incorrect; subsequent postmortem examination demonstrated that the dilated tortuous vessel was the aneurysm and its full extent was not visualized because of an intraluminal laminated clot with a reduced central channel. There was a deformed and irregular basilar artery.

The patient was discharged unimproved and remained at home in bed for three months, then gradually developed difficulty in swallowing and talking. He was readmitted with pneumonia, and a tracheotomy was necessary to remove bronchial secretions. Cerebrospinal fluid was normal except for a total protein content of 78 mg. per cent. Respirations gradually became diaphragmatic and weak, and he was placed in a respirator. He was unable to move his right side or left leg and had decreased pain sensation on the entire right side. His condition deteriorated, and he died of bulbar paralysis.

Pathologic anatomy. The heart was slightly enlarged, and there was a scar at the base of a papillary muscle of the left ventricle. Extensive pneumonia was present bilaterally. Atherosclerosis was marked in all the peripheral arterial vessels, and all the major cerebral vessels were involved. There was an enormous and complicated vertebral and basilar artery aneurysm (Fig. 4). Just above the point of entry into the posterior fossa was an angulation of the left vertebral artery with compression and distortion of the upper portion of the cord. The vessel was dilated for about 1.5 cm. above the angulation and then abruptly enlarged into a saccular aneurysm about 4 cm. in length. This was displaced far upward into the supramedullary portion of the posterior fossa, where it produced a striking compression of the lower portion of the pons. The left vertebral artery was dilated up to the junction with the right vertebral artery. The latter was dilated at the junction with the posterior inferior cerebellar artery. The continuation of the vertebral arteries into the pontine area featured an S-shaped curve which extended from right to left and reached the midline. In the interpeduncular fossa was an aneurysmal dilation of the basilar artery in the middle portion. The left vertebral artery was virtually closed at its lower point. The posterior communi-

cating arteries were rather small. The cranial nerves were markedly compressed, and the sixth nerve on the left could not be identified.

Microscopic examination. The left vertebral artery wall was almost replaced with hyaline material, and fibrous tissue and recent thrombotic material almost obliterated the lumen. The region of the hippocampus supplied by the right posterior cerebral artery showed focal sclerosis and atrophy. The midbrain and upper pons appeared intact. The inferior portion of the left cerebellar hemisphere showed recent ischemic necrosis, and the lateral plate of the medulla on the left side was infarcted. There was an old atrophy of the left corticospinal tract.

Case 5 (M.T.): This 48-year-old woman suddenly developed forceful vomiting which was associated with dull pain in both legs. Six days later, her head turned involuntarily to the left and her left arm became tonic. There were no other symptoms.

Past history revealed that she had had a positive serologic test for syphilis for twenty years with no therapy. Two years before admission, she had a thrombosis of the superior temporal artery of the left retina.

Physical examination. Blood pressure was 122/100; temperature, 37° C.; pulse, 110; and respiration, 20. The patient was alert and did not appear critically ill. The heart was enlarged to the left, and a moderately loud systolic murmur was present at the apex and base. The arterial pulses were present on the left, but only a femoral pulse was noted on the right. The right carotid pulsation was absent. The lower part of the face was weak on the left, and the tongue deviated to the right. There was marked weakness of the left arm and leg.

Laboratory data. Serologic test for syphilis in the serum was negative. The value for the nonprotein nitrogen was 118 mg. per cent. A lumbar puncture revealed clear and colorless cerebrospinal fluid. The initial pressure was 270 mm. with no cells. The cerebrospinal fluid protein content was 88 mg. per cent. Although tests for syphilis in the cerebrospinal fluid were negative, the colloidal gold test was 2233210000.

Weakness of the left arm and leg improved after admission, but, eight hours later, the patient was found dead.

Pathologic anatomy. Multiple aneurysmal dilations of the aorta were present, particularly at the arch and in the thoracic portion, with a rupture into the pericardium and resultant cardiac tamponade. The aorta and other vessels showed advanced arteriosclerosis, with changes characteristic of syphilitic arteritis. The left vertebral artery was sclerotic and dilated and contained a 2-mm. aneurysm located just before the origin of the basilar artery. The lumen of the left vertebral artery remained patent, though the sac of the aneurysm was filled with an old clot.

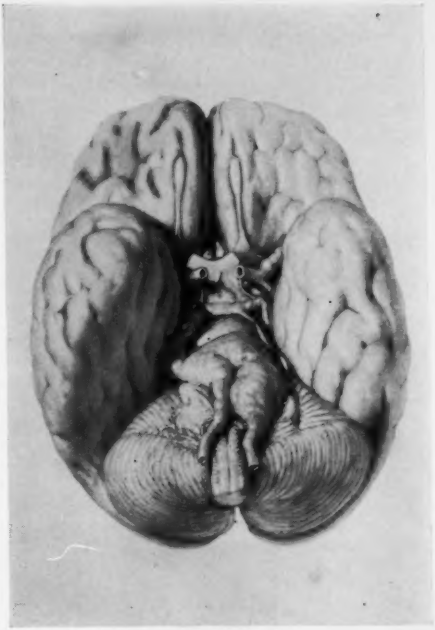

Fig. 4. Drawing by W. B. McNett of the aneurysm in Case 4

Microscopic examination of the peripheral vessels revealed only arteriosclerotic changes. The media of the left vertebral artery was fragmented in the area adjacent to the aneurysm, and elastic tissue was absent in the aneurysm and in the vessel wall adjoining it (Figs. 5 and 6). The media of the aneurysm was almost entirely replaced by blood and hyaline material. The brain and spinal cord were normal.

DISCUSSION

Pathology. Some aneurysms of the vertebral artery have been clearly related to trauma, and others may be congenital,[4] while syphilitic vascular disease is prominent in a few instances. The etiology of the majority of saccular unruptured vertebral aneurysms, however, is not clear.

Studies of the embryologic formation[5] of the vertebral arteries do not clearly establish an etiologic basis for congenital weakness of these vessels. Variations in the size of the vertebrals are reported in adults; when there is a difference in size, the left vertebral artery

is usually larger. In addition, a constriction in the left vertebral artery is sometimes observed near the union with the opposite artery.[6] It is possible that changes in vessel size, blood flow, and pressure near the union may predispose to dilation and aneurysmal formation.

In the 4 cases autopsied, arteriosclerotic changes were prominent in all vessels, including the vertebral arteries. In each case, there was hemorrhage within the intima and media. The very small saccular aneurysm in Case 5 lacked elastic tissue at the neck of the aneurysm and had arteriosclerotic changes in the adjoining areas. It is impossible to specify the relative roles of arteriosclerosis and congenital defects in initiating vertebral aneurysms. However, because the loss of elastic tissue is associated with rupture of arteriosclerotic plaques into the media in these and other vertebral arteries, our impression is that arteriosclerosis is the etiologic factor in most of the vertebral aneurysms.

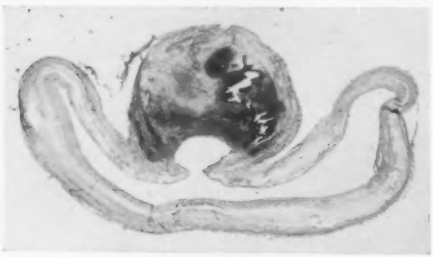

Fig. 5. Cross section of the vertebral artery and 2-mm. aneurysm in Case 5. Hematoxylin-eosin stain

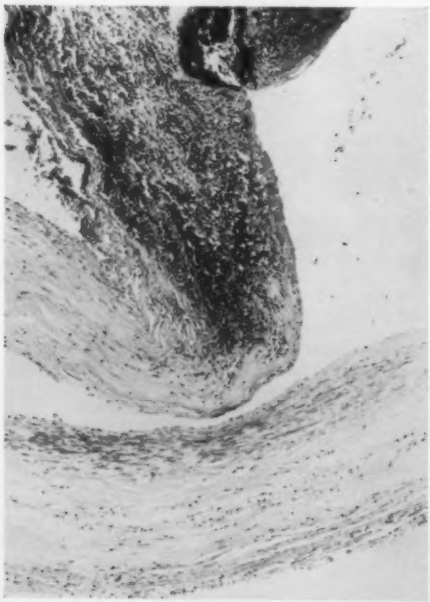

Fig. 6. Junction of aneurysm with the vertebral artery wall in Case 5. Masson stain

The aneurysm probably enlarges slowly over the years, unless it ruptures. It may be even less likely to rupture as layer after layer of laminated clot is deposited in the vessel. Periods of aneurysmal enlargement may be associated with episodes of increasing symptoms and signs. The cranial nerves are injured by traction and pressure, and later the medulla itself is severely compressed. The mass can obstruct the fourth ventricle, and the resulting hydrocephalus can produce distant neuronal changes.

In addition to direct pressure, the aneurysm probably causes destruction by producing local neuronal ischemia and anoxia. The anterior spinal artery and the posterior inferior cerebellar artery seem especially vulnerable. The former was impinged upon in Case 1. In this patient, hemorrhages and necrosis occurred in the center of the spinal cord and at operation fluid was aspirated from a cervical syrinx. In addition to destruction because of blockage of large vessels, the aneurysm can cause ischemia or stasis within small venous or arterial channels deep in the medulla and cord and produce hemorrhage or necrosis.

In some ways, the multiple episodes of minor but increasing neurologic deficits are analogous to basilar artery insufficiency. In both conditions, local temporary ischemia, secondary to impaired blood flow through the basilar system, may cause small areas of necrosis and edema. Recovery may be partial or complete.

In our 5 cases, the aneurysm was partially or largely occluded by premortem blood clot.

Clinical symptomatology. A vertebral aneurysm cannot be diagnosed from the symptomatology alone, but it can be strongly sus-

pected. The diagnosis was proved in 2 of our cases by vertebral angiography, and the diagnosis was suspected in 2 other cases. A vertebral aneurysm may have an acute or a chronic course. Some patients have no symptoms until the vessel ruptures and causes death. On the other hand, an intact vertebral aneurysm may be found incidentally at autopsy. Many patients with a vertebral aneurysm, however, have symptoms which are characteristic enough to arouse suspicion of the correct diagnosis. The signs caused by a saccular aneurysm vary with its size and location. Direct compression of the adjacent cerebellum, brain stem, and cranial nerves or impairment of the blood supply to these areas produces the neurologic signs.

Pain. A dull pain in the neck or in the back of the head is a common complaint. The suboccipital pain is usually located on the same side as the aneurysm and may be increased by movement of the head. Anterior flexion or lateral flexion of the neck to the side opposite the aneurysm may produce severe pain. Traction or compression of blood vessels near the aneurysm probably causes the increase in pain when the neck is flexed. Blood flow through vertebral arteries can be changed by movements of the neck. de Kleyn[7] has demonstrated in cadavers that cervical flexion laterally, combined with extension, compresses the vertebral vessel on the opposite side. In addition, there have been several reports of vertebral artery occlusion following chiropractic manipulation.[8] The muscles in the neck and occipital area may be tense and tender.

Mental changes. Psychosis has been reported; this, as well as mental confusion, may be episodic. Most patients will eventually show emotional lability, and occasionally generalized seizures are seen.

Cranial nerves. Some patients observe diplopia or difficulty with eye movements, and Walshe[9] has said that papilledema, nystagmus, and sixth nerve palsy are often seen. Papilledema was not prominent in our cases. The fifth and seventh nerves seem especially vulnerable. Decreased hearing and tinnitus may be present, and vertigo associated with an unsteady gait may occur. Such pressure on the eighth nerve along with involvement of the seventh and of cerebellar fibers has led to an erroneous diagnosis of acoustic neurinoma. Krayenbuhl[3] states that the presence of bilateral sixth nerve palsies may be characteristic of aneurysms in this location. Bilateral sixth nerve palsies were not noted in our cases, although at autopsy both nerves were severely stretched in Case 2. An anesthetic palate and loss of voice can occur.[10] Severe dysarthria and dysphagia appear late in the course of the disease. Bulbar compression or ischemia and respiratory insufficiency usually lead to death in the patients who do not bleed into the subarachnoid space terminally.

Motor and sensory. Usually, signs and symptoms of damage to both motor and sensory tracts are present. In addition to generalized weakness, the patient is partially paralyzed on 1 side; this complaint may precede headache. Although unilateral or bilateral paresthesia and sensory deficits occur, these are not as consistent as weakness. In fact, the relative absence of objective sensory findings has been used to distinguish between intramedullary disease and changes caused by external pressure.[10]

A wide-based gait is usually present, and the patient may fall with his eyes closed. Unilateral dysmetria may accompany the loss of equilibrium.

Tendon reflexes tend to be hyperactive on the affected side, but the Babinski sign may be present on both sides.

General. Our patients, except Case 5, had electrocardiograms indicating myocardial hypertrophy or ischemia, with signs of arteriosclerotic changes in the peripheral vessels. The electrocardiogram can perhaps be affected by traction on blood vessels at the base of the brain, but cardiograms in the cases here were not especially variable during the course of the illness. Blood pressures, however, did seem unusually labile in our cases. One patient had episodes of nausea and vomiting and an increase in neck pain in association with transient elevations in blood pressure. Another patient with severe postural hypotension observed an increase in neck pain whenever he stood up. Several patients became flushed easily and at times sweated profusely.

Though the first symptoms may appear as long as ten years before death, patients with the large saccular aneurysms finally develop

intractable nausea and vomiting, debility, and loss of weight. The patient becomes bedridden with increasing neurologic deficits. Bulbar paralysis appears, and respiratory failure with pulmonary infection was the terminal event in most of our cases.

Clinical studies. *Laboratory.* There is nothing specific in the various blood chemistry tests, though a serum cholesterol value may be of interest as evidence of arteriosclerotic disease. A serologic test for syphilis should be done on both serum and cerebrospinal fluid, since several aneurysms have been reported in patients with syphilitic arteritis. There are few reports on changes in the cerebrospinal fluid. The changes range from gross blood to xanthochromia and elevation of the total protein content. The 5 cases reported here all showed increased cerebrospinal fluid protein (60 to 220) and xanthochromic fluid.

Vertebral arteriography. In 1941, Krayenbuhl[3] was first to demonstrate a basilar artery aneurysm by vertebral arteriography. In his recent monograph, 30 more examples are listed from the literature. He reports only 1 aneurysm of the vertebral artery, though several have been demonstrated by others.[14] The interpretation of the vertebral arteriogram was misleading in Case 4. The size of the aneurysm was not apparent. The S-shaped arteriosclerotic vertebral aneurysm may be filled with laminated clot, and only the narrow tortuous central channel is seen.

Electroencephalogram. The electroencephalogram was suggestive of a posterior fossa lesion in 2 of our cases.

Diagnosis and therapy. Roentgenograms of the skull are usually normal, though a calcified aneurysm in the posterior fossa has been reported.[11] Vertebral arteriograms are indicated if surgery is contemplated.

Dandy[12] reported ligation of the extracranial portion of the vertebral artery with symptomatic relief in a patient with a vertebral aneurysm. He stated that a cure was least likely in cases of S-shaped arteriosclerotic aneurysm but did ligate 1 vertebral artery in several patients. Hamby[13] reviewed the subject and agreed that ligation was hazardous.

Logue[14] recently presented the operative results of 6 cases of posterior fossa aneurysms. Three of these were vertebral artery aneurysms. He stated that proximal clipping of the vertebral artery would reverse the flow of blood in the vessel and profoundly reduce the pressure in it. In our Case 2, the aneurysmal sac was opened and the clot was removed in an attempt to relieve the local compression on the brain stem. In Case 3, the vertebral artery was ligated intracranially without reduction in the size of the aneurysm.

SUMMARY

Five cases of saccular aneurysms of the vertebral artery are reported. These aneurysms produced symptoms of a progressive lesion in the posterior fossa, with signs of intracranial bleeding and headache in the occipital region, which was increased by movements of the neck.

Arteriosclerotic changes in the wall of the aneurysm were noted in all the cases.

Surgery was performed in 2 cases without success.

We are indebted to Dr. E. C. Kunkle for his advice and assistance. We thank Dr. G. L. Odom for permission to include Case 2.

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Noninfectious granulomatous angiitis with a predilection for the nervous system

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THE CENTRAL NERVOUS SYSTEM is only rarely affected in patients with most forms of noninfectious angiitis. In a small proportion of patients with periarteritis nodosa, the vessels of the nervous system alter as do other organs and cause hemorrhage and/or ischemic changes in the brain with neurologic signs and symptoms.[1–3]

In pulseless disease,[4] temporal arteritis,[5–7] giant cell arteritis,[8,9] and thromboangiitis obliterans,[10] the vessels of the nervous system generally escape direct involvement. However, in a few patients, pathologic changes in the great vessels of the neck induce neurologic manifestations which indicate ischemic changes in the brain.

Apparently a specific form of angiitis, generally designated as granulomatous angiitis, regularly affects the vessels of the central nervous system, at times without concurrent involvement of other organs, at times involving other organs to a less significant degree. In these patients, the clinical symptomatology is essentially neurologic; involvement of other organs, when present, generally escapes clinical attention. Cases which we believe to be of this type have been described previously by Harbits,[11] Newman and Wolf,[12] Richardson,[13] and McCormick and Neubuerger,[14] although, in some of these, other interpretations have been offered. The purpose of this paper is to present detailed observations of 2 additional cases of this nature and to suggest that the group warrants consideration as a separate clinicopathologic entity.

CASE REPORTS

Case 1. A 56-year-old woman was admitted to the hospital on October 3, 1956, because of an episode of aphasia followed by convulsive movements of the right side of the face and the right arm.

Except for the usual childhood diseases, she had not previously been ill. Onset of symptoms began early in November 1954 when she had persistent vomiting associated with frontal headaches. Physical examination at that time showed a normal blood pressure, papilledema on the right, optic atrophy on the left, a positive Romberg's sign, and normal cerebrospinal fluid. Skull x-rays showed a calcification of the posterior clinoid processes and what was thought to be a posterior displacement of a calcified pineal gland. A ventriculogram and a pneumoencephalogram revealed a normal ventricular system.

The patient left the hospital against medical advice about a month after admission. Approximately one year later, she had a second transient episode of aphasia and a sudden episode of loss of consciousness lasting thirty minutes. Examination at this time showed a visual acuity of 20/20 on the right and 20/70 on the left (corrected). The visual fields were normal; neither papilledema nor atrophy of the optic disks was observed. She continued to have intermittent episodes of headache and vomiting. In June 1956, she developed progressive weakness of both legs and had frequent falls without loss of consciousness. During the following month, she began to show gradual mental deterioration

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which was evidenced by loss of memory, disorientation, and confusion. On October 3, 1956, she had a right-sided convulsive seizure and was admitted to the hospital for the last time.

Physical examination revealed the blood pressure to be 150/80; the pulse, 78 and regular; the respiratory rate, 18; and the temperature, 100.2° F. The patient appeared disoriented for time and place, demonstrated a childish, irrational behavior, and was occasionally belligerent. She had marked memory loss, a poor capacity for calculation, and difficulty in naming objects and recognizing printed letters. Visual acuity was extemely decreased in the left eye to 20/200; she had disk pallor and a concentric constriction of the right visual field with blurring of the right optic disk. The other cranial nerve functions appeared normal. The patient had slight weakness and increased deep tendon reflexes of the right extremities, a right Babinski sign, and bilateral Hoffmann reflexes. All modalities of sensation appeared normal. No abnormalities were recognized with respect to the other organ systems.

The blood count and urinalysis and determinations for blood urea nitrogen, fasting blood sugar, serum proteins, cholesterol, cholesterol esters, serum sodium, potassium, chlorides, calcium, and phosphorous revealed normal values. Wassermann reaction was negative. The erythrocyte sedimentation rate was 35 mm. per hour. The cerebrospinal fluid examination revealed 62 red blood cells per cubic millimeter, half of them crenated; 3 lymphocytes per cubic millimeter; 88 mg. per cent of protein; a negative Wassermann reaction and colloidal gold curve; and a pressure of 220 mm. of water. The x-rays of the skull showed a questionable deepening of the floor of the sella turcica, with slight atrophy of the posterior clinoid processes, and an old postoperative defect in the right parietooccipital region. The x-ray of the chest was normal. The electroencephalogram revealed slow, 5 to 6 per second, high voltage activity in both frontal regions. The record was considered to show a diffuse abnormality more marked on the right but with no focal accentuation.

The patient became progressively lethargic, was soon unable to feed herself, and developed a frank right hemiparesis. Vomiting and headaches were not observed during the first three weeks of hospitalization. However, on October 24, she at first vomited food and, later, what appeared to be gross blood. On October 30, she had severe convulsive movements of the face and left leg and smacking movements of the lips. The movements were controlled with intravenous amobarbital sodium. A lumbar puncture disclosed a slightly xanthochromic spinal fluid under a pressure of 180 mm. of water, a protein content of 57 mg. per cent, and 363 fresh red blood cells per cubic millimeter.

The following day, the severe convulsive movements recurred and she was given intravenous and intramuscular phenobarbital sodium. The convulsive seizures were at first markedly reduced, but, after one hour, frequency increased. At this time, 0.75 cc. of paraldehyde was given intravenously without effect. She received intravenous amobarbital sodium two hours later with some, but not complete, relief of the seizures. About thirty minutes later, she suddenly became apneic and died.

At autopsy, the brain weighed 1,100 gm. Externally, the brain appeared normal except for the thickened milky appearance of the leptomeninges, particularly at the base. The left optic nerve was slightly smaller than the right. The upper 3 cervical segments of the spinal cord were available and appeared externally normal. Coronal sections revealed a fresh linear hemorrhage in the middle part of the right anterior commissure measuring 10 x 3 x 3 mm. The ventricular system was minimally dilated. The ventricular lining appeared rough and coarsely granular, particularly in the frontal horns. No other grossly pathologic changes were evident.

Microscopically, a severe granulomatous process involved arteries and veins of varying caliber, from the middle cerebral artery to the intraparenchymal vessels (Figs. 1, 2, and 3) in nearly every portion of the central nervous tissues studied. The lesions were characterized by a proliferation of connective tissue fibers and of mononuclear mesenchymal cells of varying types, including fibroblasts, lymphocytes, large mononuclear cells, and multinucleated giant cells of both the foreign body and Langhans' type (Fig. 2).

Fig. 1. Case 1. The lumen is markedly narrowed by a thickened and infiltrated intima containing a great many large mononuclear cells, many fibroblasts, many lymphocytes, and a few giant cells. The adventitial infiltrate is largely lymphocytic. (Hematoxylin and eosin × 250)

The process involved the entire thickness of the walls of some vessels, but the intimal and adventitial tissues were often more severely affected than the media, which was often spared. The intimal involvement was particularly severe in the intraparenchymal vessels, where the large mononuclear cells and giant cells were particularly abundant.

In the intraparenchymal vessels, the adventitial tissues tended to contain large numbers of lymphocytes, although large mononuclear cells and giant cells were also present. The large leptomeningeal arteries were less affected than the smaller leptomeningeal vessels and revealed a comparatively modest adventitial involvement, often with large mononuclear and giant cells predominating. The smaller leptomeningeal arteries resembled those within the brain substance. The veins were affected (Fig. 2) but, apparently, with lesser frequency than the arteries. An adventitial and perivascular granulomatous infiltration was often noted. However, it was frequently impossible to decide whether a markedly affected vessel was a vein or an artery.

Fibrinoid changes were present but in only a few of the altered vessels. The lumens of the affected vessels were often markedly

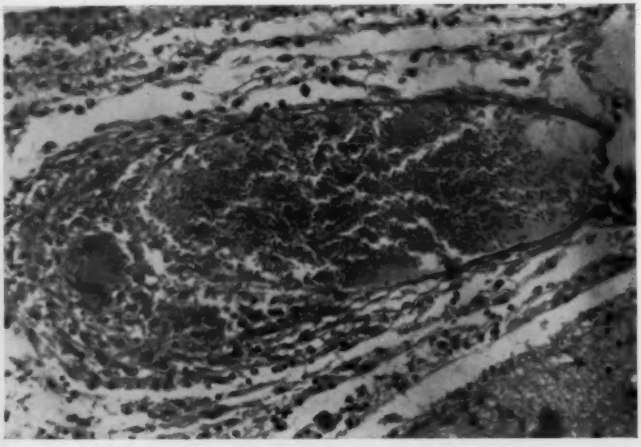

Fig. 2. Case 1. Leptomeningeal vein in cerebrum revealing a focal granuloma with a giant cell of Langhans' type. (Hematoxylin and eosin × 600)

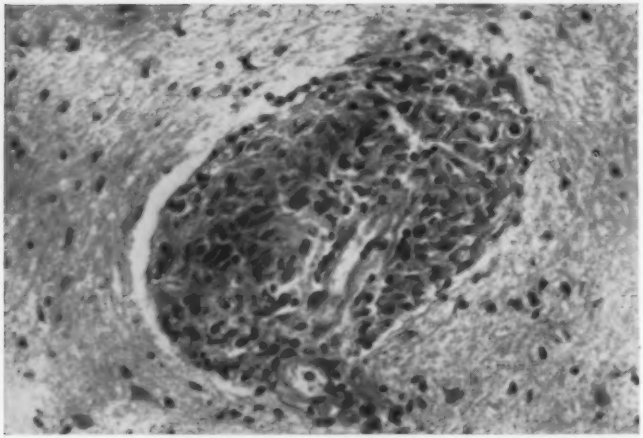

Fig. 3. Case 1. Intraparenchymal vessel with thickened granulomatous wall and narrow lumen. (Hematoxylin and eosin × 800)

narrowed or completely occluded (Fig. 3). The process was particularly severe in the leptomeninges, the subependymal white matter of the cerebrum, the tegmentum of the brain stem, and in the cerebellum; but no portion of the central nervous tissues was spared.

Lesions were observed in the sixth cranial nerve and in the optic chiasm. The cerebellum revealed a large, focal, old, cystic infarct (Fig. 4), and additional areas demonstrated a loss of Purkinje and granular cells and a proliferation of Bergmann astrocytes. Typical fresh infarcts were not noted in the cerebrum, brain stem, or cord, but many areas within these structures appeared rarefied; showed nonspecific neuronal changes, including rare necrotic neurons and moderate neuron loss; and had a marked, reactive astrocytosis. These are probably ischemic changes. The hemorrhage in the anterior commissure was recent. No fungi, tubercle bacilli, or other bacteria were demonstrated with special staining procedures.

Study of the other organs revealed no lesions resembling those in the brain. The only abnormalities noted were an old renal infarct, pulmonary edema, and the presence of emboli

Fig. 4. Case 1. Old cerebellar infarct. (Hematoxylin and eosin × 75)

in some small branches of the pulmonary artery.

Case 2. The patient, an 18-year-old youth, was admitted to the hospital for the third time on June 2, 1953, nineteen days prior to his death. He had numbness of the left side of the body and speech difficulties. The patient had had diabetes mellitus since 1940, when he came to the hospital because of weight loss, polyuria, and polydipsia. He was discharged on a special diet and told to take 10 units of protamin-zinc-insulin daily. In 1945, he was admitted a second time for diarrhea of undetermined origin which subsided during hospitalization. At that time, his diabetes was well controlled, although the dosage of insulin had gradually been increased from 10 to 85 units daily. For much of his life, he presented a problem of disorderly behavior and lived in a poor social environment.

During the first week of May 1953, about six weeks prior to his death, he began to complain of left temporal headaches and appeared to his family to be less alert than usual. By the end of the month, he had become drowsy and complained of progressive generalized weakness and stiffness and numbness of his left extremities. By June 1, 1953, he had developed horizontal diplopia for distant objects which was more pronounced on right lateral gaze and numbness of the left side of his face. The following day his voice became weak, and he was hospitalized.

On admission, his blood pressure was 140/90; pulse rate, 128 per minute; and temperature, 99° F. He appeared drowsy and was slightly disoriented for time.

The optic fundi and the visual fields were normal. The pupils appeared normal in size and shape and reacted well to light. He had slight ptosis of the right eyelid and a horizontal diplopia on right lateral gaze but no gross weakness of gaze or of individual eye muscles. Unsustained nystagmus was noted on right lateral and upward gazes. A mild left hemiparesis involving the arm, leg, and face, in approximately that order of severity, was also noted. The distal segments of the limbs appeared weaker than the proximal. The left biceps jerk was greater than the right. Both knee jerks were absent. The right ankle jerk was depressed, while the left appeared absent. There was a left Babinski sign. All modalities of sensation with both single and double simultaneous stimuli appeared normal.

A complete blood count was normal. The erythrocyte sedimentation rate was 27 mm. per hour. Examination of the urine revealed a specific gravity of 1.010, 2+ sugar, no acetone or diacetic acid, and 2 to 3 red blood cells per high-power field. The blood Wassermann was negative. The fasting blood sugar was 420 mg. per cent. The blood urea nitrogen, carbon dioxide combining power, serum electrolytes, serum proteins, and cholesterol and its esters were of normal value. The cerebrospinal fluid pressure was 180 mm. of water. The spinal fluid contained 2 lymphocytes per cubic millimeter, 17 mg. per cent protein, and 98 mg. per cent sugar. The spinal fluid Wassermann and colloidal gold curve were negative. The skull and chest x-rays were normal. The electroencephalogram was considered diffusely abnormal—showing low voltage slow activity accentuated posteriorly—more so on the right side.

Approximately one month after onset and fourteen days before death, the patient complained of blurred vision and his diplopia became prominent in all directions of gaze. Nystagmus on left and upward lateral gazes was also noted. At this time, however, his hemiparesis had improved. Amobarbital sodium (0.4 gm.) was given intravenously and produced severe disorientation, confabulation, and denial of illness which suggested diffuse cerebral dysfunction.

The patient had become increasingly depressed and lethargic and showed severe dysphagia and dysarthria eight days prior to death. The right palpebral fissure was greater than the left. He had marked palatopharyngeal paresis, absence of the gag reflex, dysphonia, and a high-pitched voice. He was unable to protrude his tongue easily. In addition to the hypertonic left hemiparesis, he had some weakness of the right upper extremity. Sensation remained intact. During the last seven days of his life, the disease progressed very rapidly. Bilateral palpebral ptosis, a sensory deficit over the right lower extremity, bilateral Babinski signs, diplegia which rapidly evolved to quadriplegia, palatoplegia, and weakness of the jaw and facial

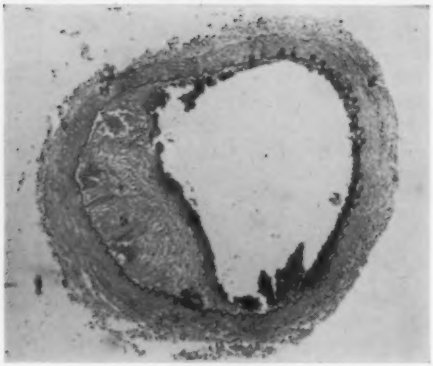

Fig. 5. Case 2. Middle cerebral artery. An eccentric granulomatous plaque in the intima is composed of large mononuclear cells, lymphocytes, and multinucleated giant cells of a foreign body type. The lumen is narrowed. The elastica and media are normal. The adventitia is infiltrated by lymphocytes.

musculature were apparent. An adequate airway became difficult to maintain. The patient became comatose, his blood pressure rose to 160/70, his temperature to 106° F., and he died on the twentieth hospital day.

At autopsy, the brain weighed 1,200 gm. No external abnormalities were found except for an unusual opacity of some of the large arteries, particularly the anterior spinal artery. Leptomeningeal congestion was also seen. Coronal sections revealed areas of infarction involving the right occipital lobe, the left temporoparietal area of the cerebrum, and the left side of the base of the midpons and medulla. These lesions were soft, dusky, and irregular in contour; those in the cerebrum revealed an obscuration of the corticomedullary junction. No other gross changes were recognized.

Microscopically, the areas of infarction revealed the characteristic rarefaction, parenchymal disruption, punctate hemorrhages, focal infiltration of polymorphonuclear leukocytes, and more marked and more widespread proliferation of microglial phagocytes and homogenizing necrosis of neurons.

The primary changes were in the walls of the blood vessels and resembled the changes described in Case 1 (Figs. 5, 6, and 7). A striking characteristic in this instance was the localization of the process to the intima of major vessels, such as the middle cerebral artery (Fig. 5) where it formed a sharply localized projection into the lumen which caused narrowing. Some of the arteries were occluded by bland thrombotic material, and, in some instances, giant cells and mononuclear cells indicated that an intimal granuloma was the site of the thrombosis. A few granulomas of like character were present in the dura. In other respects, the microscopic changes in the brain were like those described for Case 1 (Figs. 6 and 7).

The lungs revealed a severe lobular pneumonia, thromboembolic material in some of the vessels, and small granulomas like those in the brain about some of the smaller arteries. The heart had numerous granulomata around the epicardial vessels, within the endocardium, in the myocardium, in the intima of the aorta and pulmonary artery, and in the media of the pulmonary artery. Thrombotic material was present over the lesions in the pulmonary artery. Lymphocytes extended from the focal myocardial lesions into the adjacent interstitial tissues. Granulomas of such character were present in the lymph nodes, spleen, serosa of the stomach, and the liver. In the liver, some of the lesions were characterized by central necrosis surrounded by mononuclear cells in a palisading fashion. The kidney revealed a gross infarct and hyaline arteriolar changes, some of which extended into the glomeruli. Fungi, tubercle bacilli, and other bacteria were not demonstrable with special staining technics.

DISCUSSION

Our opinion is that the 2 cases described here and the other 6 collected from the literature (see table)* should be grouped together as delineating a distinct clinical and pathologic entity which may be designated noninfectious granulomatous angiitis with a predilection for the nervous system. It is recognized that the delineation of such an entity within the group of diseases characterized by a generalized noninfectious arteritis must be considered tentative until the etiology and pathogenesis of the various forms of these types of angiitides are

*See also footnote at end of article.

established. Nevertheless, the pattern of the disease process here described does appear to segregate this form from the other forms of noninfectious arteritis.

Perhaps the most striking point of distinction is that, in each of the patients considered in this paper, the disease process involved the central nervous system predominantly. In 4 patients no concomitant involvement of any other organ of the body occurred, while, in 2 patients, such visceral involvement was present, although less extensive and less severe. In 2 patients, autopsy was limited to the central nervous system. In all 8, the clinical features were essentially neurologic; no clear clinical evidence of the visceral involvement was found, even in the 2 patients in whom such involvement was demonstrated pathologically. The nature of the essentially granulomatous process serves as another feature common to the cases enumerated and distinguishable from the other forms of arteritis.

Pulseless disease (Takayashu)[4,5] appears to be a clinical syndrome frequently affecting young women and is due to involvement of the major branches of the arch of the aorta, such as the subclavian or the carotid arteries, by granulomatous processes of various types, some of which are clearly luetic. When central nervous system involvement in pulseless disease does occur, it is the result of narrowing of the carotid arteries in the neck. No patient, to the best of our knowledge, has shown evidence of involvement of the intracerebral vasculature.

The involvement of the intracranial arteries by thromboangiitis obliterans (Buerger's disease), has been considered frequent by some[16] and nonexistent by others.[17] In a report describing this condition in the nervous system,[18] it is stated that the lesions bear no histologic resemblance to the lesions which characteristically involve the vessels of the extremities in thromboangiitis obliterans and that the process may be limited to the vessels of the nervous system. In these circumstances, the identity of the cerebral process described with the characteristic thromboangiitis obliterans of the extremities may be considered uncertain.

In temporal arteritis (cranial arteritis, giant cell arteritis), the temporal artery alone is involved in most instances,[5,19,20] although sometimes other branches of the aorta are involved as well.[9,21] The temporal artery is spared in some cases.[8] Involvement of the nervous system is rare, and, when it does occur, it is generally due to involvement of the common or

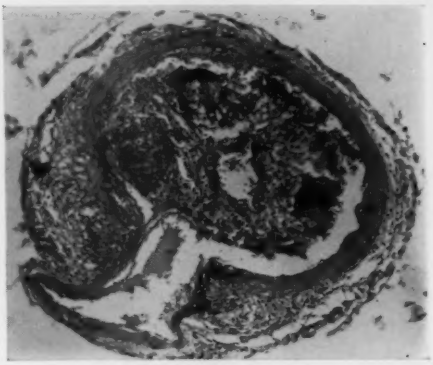

Fig. 6. Case 2. Leptomeningeal vessel about medulla. The lumen is almost completely obliterated by a cellular granulation tissue containing multinucleated giant cells of the foreign body type; 2 adventitial granulomas are present as well. (Hematoxylin and eosin × 400)

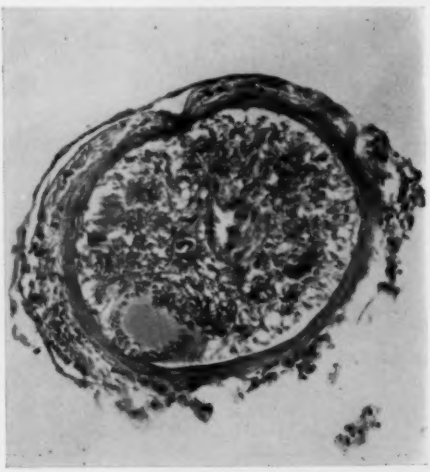

Fig. 7. Case 2. Leptomeningeal vessel about medulla. The lumen is almost completely filled as a result of a marked cellular proliferation in the intima. A Langhans' giant cell is present. The media is relatively preserved. (Hematoxylin and eosin × 500)

Case:	1	2	Harbitz [11]	Newman & Wolf Case 1 [12]	Newman & Wolf Case 2 [12]	Richardson [13]	McCormick & Neuberger Case 1 [14]	McCormick & Neuberger Case 2 [14]
Age	18	56	26	middle-aged	elderly	64	50	55
Sex	M	F	F	M	M	M	F	F
Duration	6 weeks	2½ years	2 years	6 weeks	2½ years	5 weeks	9½ months	3 days
Hypertension	0	0	0	0	0	•	0	0
Allergy	0	0	0	0	Asthma	0	0	0
Headache	•	•	•	▪	•	•	▪	
Convulsions	•	0	•	0	0	•	▪	
Stupor-Coma	•	•	•	0	0	•	•	•
Multifocal CNS signs	•	•	•	•	•	•	▪	•
Remissions	•	0	•	0	•	0	•	0
CSF protein (mg. %)	88	17			100	62	92	130
CSF lymphocytes	3	2			55–432	49	40	55
EEG abnormality	diffuse	diffuse				diffuse		
Other viscera	•	0			•	0	0	0

• indicates the known presence and 0 indicates the known absence of the feature indicated. A blank space indicates the absence of data. The heading, Other viscera, indicates the presence or absence of lesions in other viscera as disclosed by autopsy.

internal carotid arteries with consequent narrowing and occlusion or occasionally with the formation of thromboemboli. The number of cases in which the intracranial vessels are reported to have been involved is very small and, in some of these reports,[22,23] pathologic data is incomplete. Temporal arteritis is an entity which characteristically affects elderly people and appears generally to be a self-limited, nonfatal process. Temporal arteritis takes the form of a granulomatous panarteritis predominantly affecting the media and associated with necrosis and thrombosis. The media is often spared in granulomatous angiitis. When the process affects the carotid arteries, carotid insufficiency or occlusion may result and death may occur.[6,21]

Cases 7 and 8 in the group of granulomatous angiitis of the nervous system were interpreted by those reporting them[14] as giant cell arteritis (temporal arteritis). In the light of the skill and experience of those making the report, we are naturally hesitant to offer an alternative interpretation. However, we are encouraged to do so by their stated opinion that the involvement of the small meningeal and intracerebral vessels in these patients seems unique among cases of temporal arteritis. The similarity of these 2 patients to the others listed in the table appears to us to be much greater than their resemblance to temporal arteritis. In both, the temporal arteries were spared, while the predilection for the nervous system was very marked. There was only mural thickening of the left subclavian and axillary arteries in 1 patient, and no extracranial involvement in the other.

Periarteritis nodosa may be distinguished by the infrequent involvement of the brain, even in cases of widespread visceral involvement.[1,24] When the cerebral vessels are involved, a fibrinoid alteration is prominent, a change which is rather infrequent and not intense in granulomatous angiitis of the nervous system. Granulomatous changes in periarteritis nodosa are much less marked. Hypersensitivity angiitis, which some would distinguish from periarteritis nodosa with which it has been grouped, is described in many reports as a rapidly fatal process. Hypersensitivity angiitis is assumed to be a manifestation of

allergy, often to sulfonamides or other substances.[25,26]

Pathologically, the resemblance of the lesions of granulomatous angiitis of the nervous system to those reported as allergic granulomatosis[27] is noteworthy. As reported by Churg and Strauss,[27] this condition is invariably associated with bronchial asthma, and the arteritis is assumed to be a manifestation of hypersensitivity. As can be seen in the table, asthma was present in only 1 of the patients grouped as granulomatous angiitis. One of us (I.F.) has had occasion to examine the 4 available brains of the original Churg and Strauss series of allergic granulomatosis. None of these brains showed vascular lesions comparable to those present in the viscera and skin. On the other hand, Dr. Strauss had an opportunity to examine the second case of the present report and expressed the opinion that the lesions were not precisely identical to those in the cases she had originally reported as allergic granulomatosis. Nevertheless, the lesions in these 2 processes are so similar that Newman and Wolf[12] appear entirely justified in calling attention to the resemblance of the lesions in their 2 patients (Cases 3 and 4 of the table) to those of allergic granulomatosis, particularly since 1 of their patients had had bronchial asthma and the other a dermatitis that could have been allergic in nature.

Sarcoidosis (Boeck) of the central nervous system is quite rare[28] and generally assumes the form of a diffuse granulomatous leptomeningitis or less often, of circumscribed large granulomas within the brain substance.[29,30] Evidence is usually found of involvement of other viscera as well.[28] In general, this disease of connective tissues does not primarily involve blood vessels. In the leptomeninges, and, certainly, within the brain substances, the lesions—if small enough—would lie in relation to the walls of blood vessels, the major sources of connective tissues in the brain. Some of these lesions may resemble the lesions of the granulomatous angiitis of the nervous system.[30] None of the more common lesions of sarcoid were present in the cases listed in the table.

A form of cerebral hyalinosis exists which affects the cerebral arteries of hypertensive patients and which may be the basis for the cerebral hemorrhage noted in this connection.[31] However, such lesions are less frequent, show much more fibrinoid change and greater inflammatory reaction, and appear uniformly associated with hypertension. This seems to be the only other arteritic process, apart from the disease entity suggested here, which shows a predilection for involvement of the central nervous system.

The cases listed in the table reveal a disease pattern different from the other arteritic processes just enumerated. They show a predominant and often exclusive involvement of the vessels of the central nervous system by a severe, widespread, granulomatous inflammation. The inflammatory infiltrate contains many lymphocytes and fibroblasts, a rare eosinophil, many giant cells of both the foreign body and the Langhans types, and a considerable deposition of connective tissue fibers.

The lumen of the vessels so affected appear markedly narrowed, and ischemic lesions are noted in the adjacent neural tissues. Rarely, small hemorrhages are also present. The granulomatous process sometimes involves the major intracranial vessels, but, more characteristically, the process involves the smaller meningeal and parenchymal vessels. The arteries are predominantly affected, although involvement of veins is also clearly present. The pathologic process may affect only the intima, this change being noted particularly in the large vessels. It may involve the intima and the adventitia, sparing the media. Most frequently, it affects the entire thickness of the vessel wall. The granulomatous process may be very extensive, and, at times, confluence of lesions in adjacent vessels is readily appreciated. Occasionally, the granulomatous lesions are noted in the meninges without obvious relationship to blood vessels. Visceral involvement, when it occurs, resembles the lesion in the nervous system, although occasionally there are large lesions of the extravascular tissues, such as the necrotic hepatic lesions noted in Case 2.

The nature of the granulomatous arteritis described here is no less obscure than that of the other forms of noninfectious arteritis previously discussed. The evidence for hypersensitivity states, so often implicated in these conditions, is largely inferential. In the cases of granulomatous angiitis cited, hypersensi-

tivity was not manifest in any consistent and clearly recognizable form. Arterial hypertension, implicated in some other forms of arteritis, was absent in most instances. Infectious agents, such as tubercle bacilli, fungi, and parasites, were not demonstrated. Indeed, we have not been able to recognize any factor which might suggest a pathogenic mechanism for this process. In this circumstance, the delineation of this entity by virtue of its specific involvement of central nervous tissues and its granulomatous character may be considered provisional.

Granulomatous angiitis of the nervous system affects individuals of all ages but perhaps most frequently affects those of middle age. In this series, the youngest patient was 18, the oldest, 64. Both sexes were equally affected. After onset, the disease was fatal in three days in 1 patient, in less than six weeks in 3 patients, and in two to two and one-half years in 4. In all patients, the clinical manifestations were referable to the nervous system. The symptomatology was that of a diffuse disorder of the central nervous system with some focal accentuation. In this series, the focal accentuation of symptoms indicated disease most marked in the cerebrum in 5 patients, in the brain stem in 1, and in the spinal cord in 2. The salient clinical features included headaches of intermittent nature, slight fever, organic mental syndrome, convulsive seizures, somnolence, and lethargy. In addition, there was frequent impairment of cranial nerve functions, speech disturbances, aphasia, hemiparesis, paraparesis, and various forms of sensory deficits. These manifestations varied from patient to patient according to the localization of the arteritic process. A slight to moderate leukocytosis was found in the peripheral blood. The cerebrospinal fluid usually contained an increase in protein and a moderate pleocytosis, usually of lymphocytes, and the fluid sometimes appeared xanthochromic. The electroencephalogram was usually diffusely abnormal. The pneumoencephalogram was normal in most patients or showed a slight dilation of the ventricular system in a few.

The disease has been confused with neoplasm, multiple sclerosis, and toxic or metabolic disorders. Because neoplasm was suspected, 3 of the 8 patients discussed here had exploratory craniotomy with negative results.

The symptomatology of granulomatous angiitis of the nervous sytem is varied and confusing. Perhaps this process should be considered among the diagnostic possibilities in those patients in whom a protean neurologic symptomatology does not permit a definite diagnosis of a more common disease process. This possibility may warrant particular consideration in those obscure neurologic cases in which some of the clinical features suggest tumor. If a surgical exploration fails to disclose tumor, biopsy of nonneoplastic tissues might reveal the vascular lesions of this process and establish the diagnosis.

In regard to therapy, we have no specific suggestions to offer, except to recall that cortisone and ACTH have apparently effected improvement in some arteritic conditions of similar noninfectious character.

SUMMARY

Granulomatous alteration of the vessels of the central nervous system is described in 2 patients. In 1, the process was limited to the brain; in the other, visceral involvement was also present, although to a less significant degree. Attention was directed to the occurrence of 6 other cases found in the literature which resembled these patients clinically and pathologically. In all these patients, predominant and, at times, exclusive involvement was found of the vessels of the nervous system by a granulomatous angiitis which involved both arteries and veins—although the arterial lesions predominated.

The process essentially consisted of a proliferation of various mesenchymal cells in the intima, the adventitia, or in all layers of the vessel wall. Giant cells of the Langhans or foreign-body types were prominent among these infiltrating cells. The clinical picture was that of a nervous system disorder of a diffuse nature with some focal accentuation. In no instance was there clinical evidence of involvement of organs other than the nervous system. It is suggested that these cases warrant consideration as an entity, distinct from other forms of generalized arteritis, and that these be designated as granulomatous angiitis with a predilection for the central nervous system.

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FOOTNOTE

As this paper was being completed, we were given the opportunity of examining sections of a very similar case which will be reported separately by Dr. John Moossy of the Louisiana State University School of Medicine.

A 30-year-old woman died after an illness of approximately three months, during which time she experienced multiple episodes of neurologic character which were interpreted to be of vascular origin. At autopsy, vascular lesions like those being discussed in this paper, were present in the brain. No similar lesions were found in other organs. We are grateful to Dr. Moossy for showing these sections to us.

Attention may also be directed to the case reported by Zellinger and von Meyerberg in Schweizerische medizinische Wochenschrift (72:825-826, 1942) of a 21-year-old man with neurologic abnormalities, "like those of multiple sclerosis." Histopathologic study of the brain showed multiple perivascular granulomas which included giant cells. A calcified primary tuberculous nodule in the lung is also described. The case was thought to be tuberculous in character, possibly Boeck's sarcoid, the latter being considered a form of tuberculosis. Although the data are incomplete, the case does resemble those reported here.

Electroencephalograms during coma

Normal and borderline records in 5 patients

Carlo Loeb, M.D., Guido Rosadini, M.D., and G. F. Poggio, M.D.

In a previous work,[1] one of us (C. L.), demonstrated that patients in a state of coma may display a variety of patterns of electroencephalographic activity. It has been shown, in fact, that the frequency, form, reactivity, and spatial distribution of the bioelectric rhythms, including a rather regular alpha activity, may vary in comatose patients.[2–6]

Reversion of an abnormal electroencephalogram to a completely normal one or to a record closely resembling normal has been known to occur in various conditions associated with coma. For instance, the attenuation or even abolition, a few days before death, of the diffuse, continuous slow waves observed in patients with subacute necrotic encephalitis has been seen in the face of an apparently unchanged general condition.[7] A similar change to a normal record has been observed in some patients in deep coma a few hours before death.[6] Such a reversion has also occurred in patients with psychomotor epilepsy in the midst of an acute psychotic attack.[8,9]

A clinical, electroencephalographic, and pathologic study has been made of 5 comatose patients. All showed, during coma, normal or borderline electroencephalographic activity. This study contributes a further description of electroencephalographic records during coma and also offers an opportunity to discuss interpretation of normal or borderline electroencephalographic records in these cases.

METHOD

Technic. Electroencephalograms were made in 5 patients selected from a series of 30 comatose patients who were investigated from clinical, electroencephalographic and anatomical standpoints. (Reference to the 25 patients who had electroencephalographic changes has been made previously.[1]) An 8-channel Alvar or a 10-channel Galileo Beta instrument and the 10 to 20 system of electrode placements recommended by the International Federation was used. During the recording, auditory (noise and/or whistle), visual (opening and closing of the eyes done by manually holding the patient's eyelids), and noxious (pinprick, compression of the eyeball) stimuli were applied to all the patients of this series and, in most cases, a flicker stimulus was applied as well. Whenever possible, records were made of the same patient in different degrees of coma.

The brain of each patient was examined post mortem, and a complete autopsy was performed on 2. The site of the cerebral lesion was reconstructed on the basis of macro- and microscopic sections.

Classification of comatose patients. The intensity of the coma observed in patients varies in a continuous spectrum from the very deepest, in which death approaches, to the very lightest, in which the patient is semiconscious. For convenience, comatose patients may be divided into 3 groups: light coma (C1), moderate coma (C2), and deep coma (C3). The parameters used for such a classification are the concurrent signs and symptoms commonly found in comatose patients.[1] All patients in this series were in deep coma (C3).

RESULTS

The site and type of the cerebral lesions found in our patients are indicated in the table.

The essential data concerning our observations can be summarized as follows:

Case 1. (Subdural and epidural right hematoma.) This 49-year-old woman was involved in a street accident ten hours before admission

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SITE AND TYPE OF CEREBRAL LESIONS IN 5 COMATOSE PATIENTS

Type and location of the cerebral lesion	Electroencephalogram: Fast rhythm, low voltage	Electroencephalogram: 9 c/s	Reactivity: +	Reactivity: ±	Reactivity: —
Subdural right hematoma (Case 1).	1				1
Spongioblastoma in the right cerebellar hemisphere (Case 2).	1			1	
Pontine hemorrhage (Cases 3 and 4).		2	2		
Subacute necrotic encephalitis (Case 5).		1			1
Total	2	3	2	1	2

+ good response ± minimal response — no response

and immediately lost consciousness. On admission, the patient was in deep coma (C3) with Kussmaul respiration and urinary incontinence. The neurologic examination revealed absence of the deglutition and pupillary reflexes, spasticity of all 4 extremities, and no reaction to painful stimuli, however intense. Her coma lasted six hours.

The electroencephalogram taken during the second hour of coma showed a diffuse, low-voltage, fast activity and no reactivity to sensory stimuli.

Autopsy revealed the presence of subdural and epidural hematomata on the right side and right temporobasal and right parietooccipital fractures of the skull.

Case 2. (Spongioblastoma of the right cerebellar hemisphere.) This 45-year-old man had had intracranial hypertensive syndrome for seven days. A day before admission, he suddenly dropped into a deep coma. On admission, he was still in deep coma (C3), without modification of respiration. Neurologic examination revealed absence of the deglutition and pupillary reflexes, hyperactivity of deep reflexes of the left side, and bilateral Babinski's sign. He made no response to painful stimuli, however intense. His coma lasted twenty-four hours.

The electroencephalogram taken during the sixth hour of coma revealed a diffuse, continuous, low-voltage, fast activity. Immediately after closing the eyes (done by manually holding the patient's eyelids), some activity occurred at 8 to 9 c/s which lasted a few seconds. Sometimes, during the opening of the eyes, a rather regular, but inconstant, activity occurred at 8 to 9 c/s.

At necropsy, a large spongioblastoma was found which occupied almost the entire right cerebellar hemisphere.

Case 3.* (Pontine hemorrhage, Figs. 1 and 2). This 57-year-old woman had had severe arterial hypertension for several years and signs of heart failure for some four to five years. She lost consciousness abruptly two hours before admission, having previously had paresthesias in the 4 extremities. On admission, she was in deep coma (C3) with stertorous respiration and incontinence of the sphincters. Blood pressure was 220/120 and pulse, 85.

Neurologic examination showed a generalized flaccidity, hyporeflexia of the arms, relative hyperreflexia of the legs, response to compression of the eyeball, bilateral positive Babinski's sign, right spinal synergia, anisocoria, greater on the right than on the left side. Her coma lasted thirty hours.

The electroencephalogram taken six hours after the onset of coma showed a rather regular activity of 100 microvolts at 8 to 9 c/s with some low-voltage fast activity, mainly bifrontal, and occasionally diffuse bursts at 3 to 4 c/s and negative diphasic spikes. The opening of the eyes (manually done by the examiner) showed, for a few seconds, a low-voltage, fast activity; closing of the eyes was followed by a slight increase of the voltage of the activity at 8 to 9 c/s. Bilateral driving of the cerebral rhythms by flicker could be ob-

*This case has been referred to previously.[2] Our incomplete description of the electroencephalographic record of this case led some authors[10,11] to the conclusion that the electroencephalogram could not be affected by sensory stimulation. In fact, we were able to demonstrate that the electroencephalographic record of this patient could be driven by flickering visual stimuli, and we now add that a blocking reaction was evoked by simple opening of the eyes (done by manually holding the patient's eyelids).

tained. At necropsy, a large hemorrhage was found in the upper two-thirds of the pons—extending up to the pontomesencephalic junction.

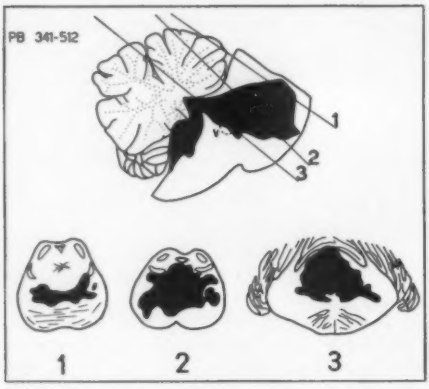


Fig. 1. (Case 3.) Diagrammatic outline of the extent of the hemorrhage in the brain stem

Case 4. (Pontine hemorrhage, Figs. 3 and 4). This 54-year-old woman had had arterial hypertension for several years, and, ten hours before admission, she abruptly lost consciousness. Examination revealed a state of deep coma (C3), with stertorous respiration, slight arterial hypertension (170/80), and urinary incontinence.

Neurologic examination showed the absence of the deglutition and pupillary reflexes, marked increase in muscular tone, and hyperactivity of the deep reflexes of the 4 extremities, left Babinski's sign, and no response to painful stimuli. Coma lasted thirteen hours.

The electroencephalogram, taken two hours after the onset of coma, revealed a rather regular activity at 9 c/s, 40 to 50 microvolts in amplitude, with good reactivity to visual stimuli.

Necroscopy showed a large hemorrhage located in the upper-third of the pons. A small hemorrhage in the base of the left peduncle was also seen.

Case 5. (Acute necrotic encephalitis). This

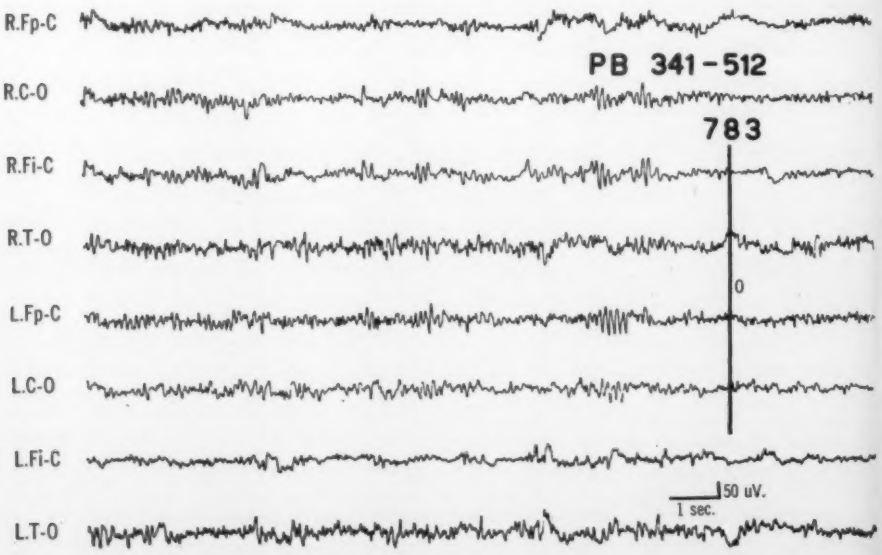


Fig. 2. (Case 3.) Electroencephalogram taken six hours after the onset of coma (C3) shows a rather regular activity at 8 to 9 c/s, 100 microvolts, occasionally diffuse bursts at 3 to 4 c/s, and negative and diphasic spikes; good reactivity to visual stimuli (o = opening of the eyes done manually by holding the patient's eyelids).

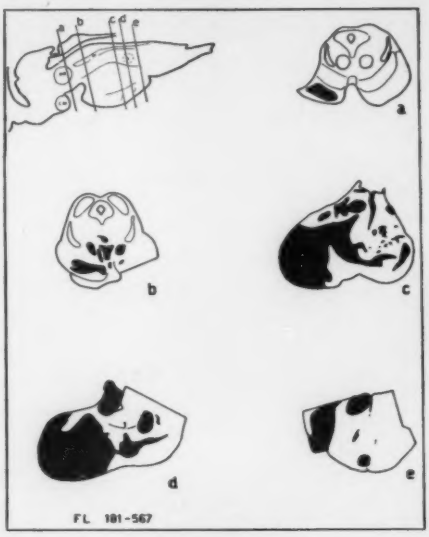


Fig. 3. (Case 4.) Diagrammatic outline of the extent of the hemorrhage in the brain stem

32-year-old man had no symptoms until four days before admission. At that time, he showed a slight left hemiparesis when he awoke, which was followed twenty-four hours later by deep coma. On admission, the patient was still in deep coma (C3). Blood pressure was 165/100.

Neurologic examination revealed a left hemiplegia, bilateral Babinski's sign, and no response to painful stimuli. Coma lasted four days.

The electroencephalogram taken on the third day of coma showed a rather regular activity at 8 to 9 c/s, 30 to 40 microvolts in amplitude, and some occasional isolated waves at 4 to 5 per second. No reactivity to visual or painful stimuli was seen (Fig. 9).

Microscopic examination of the brain chiefly showed the following features: necrotic foci,

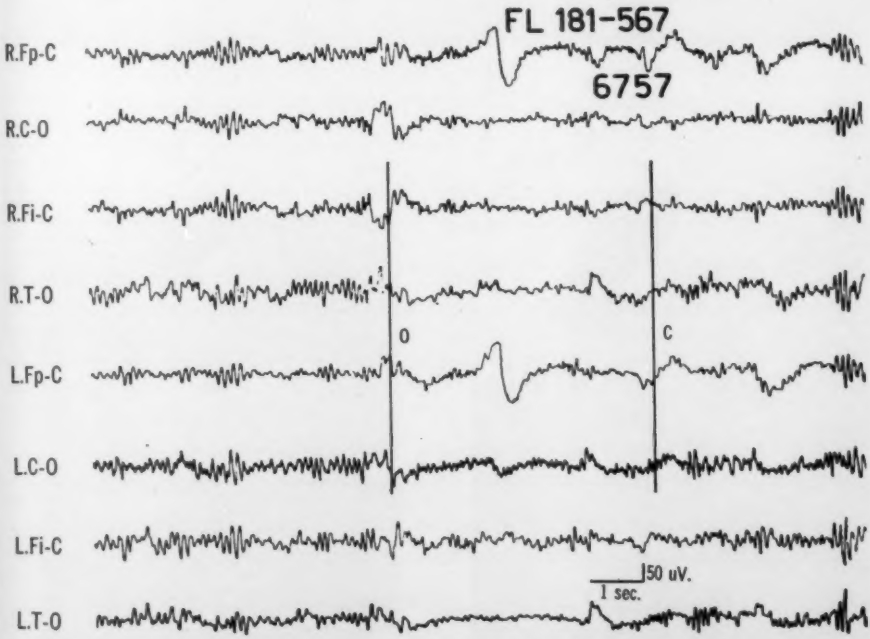
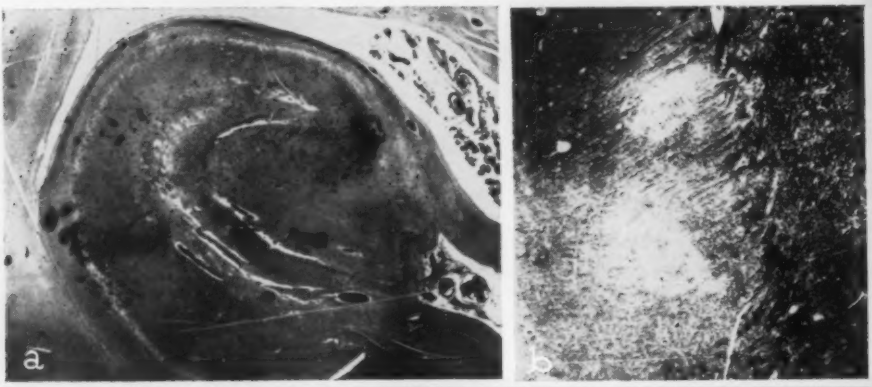


Fig. 4. (Case 4.) Electroencephalogram taken the second hour after the onset of coma (C3) shows a rather regular activity of 100 microvolts at 9 c/s and a good reactivity to the visual stimuli (o = opening and c = closing of the eyes done by manually holding the patient's eyelids).

Fig. 5. (Case 5.) Diagrammatic outline (*left*) of the necrotic and hemorrhagic areas in the diencephalon and telencephalon. Microscopic appearance in Weil preparations of hemorrhagic infarction in the right hippocampus (a) and of the demyelinized area in the ventrobasal right thalamus (b). (× 10)



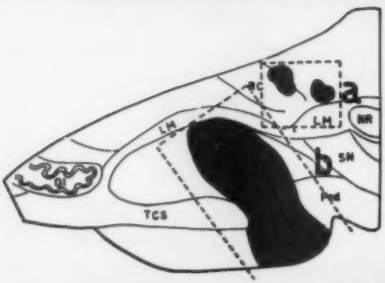
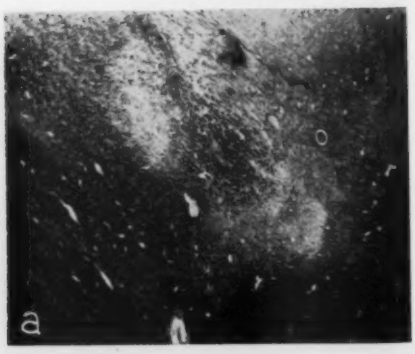


Fig. 6. (Case 5.) Diagrammatic outline (*left*) of the necrotic foci in the brain stem and their microscopic appearance in Weil preparations (a and b). (× 10)



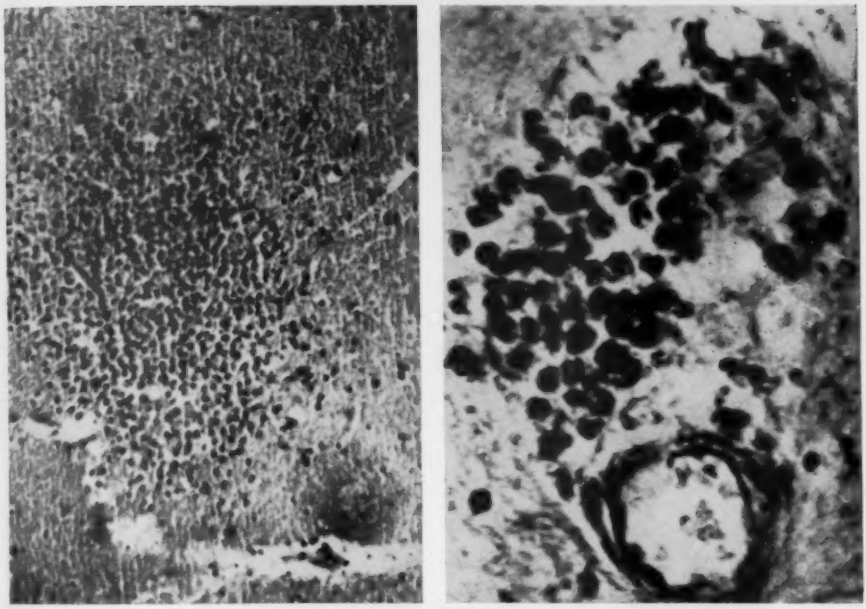


Fig. 7. (Case 5.) (*Left*) Area of nodular gliosis. (*Right*) Perivascular infiltration in the right hippocampus. Hemalum hematoxylin and eosin × 60 (*left*) and × 500 (*right*)

hemorrhagic extravasations, and basal meningitis. Necrotic foci of 2 types were found: areas of demyelinization located in the right ventrobasal region of the thalamus and bilaterally in the upper third of the pons (Figs 5 and 6), where glial and mesenchymal reactions were lacking, and disseminated areas of softening infiltrated by lymphocytes, macrophagic cells, and microglial elements evolving into granular bodies, and occasional polymorphonuclear leucocytes. The areas of softening were surrounded by perivascular infiltration and by nodular foci of glial infiltration (Fig. 7). No inflammatory signs or diffuse gliosis was seen. The massive hemorrhagic infarction was chiefly located in all sectors of the hippocampus bilaterally (Figs. 5a and 8a, *left*). The meningeal alterations were patchily distributed and were predominant on the basal surface of the brain. Vascular lesions—such as congestion, diapedesis, and, occasionally, thrombosis—parvicellular infiltration, especially perivascular (Fig. 8, *center* and *right*) and free in the tissue, and edema are the most consistent features.

DISCUSSION

It is evident from the material presented above that deep coma may indeed be accompanied by electroencephalographic activity which has a normal or borderline appearance —a finding that obviously modifies the old view that deep coma is always characterized electroencephalographically by diffuse slow rhythms. Moreover, our observations, when considered together with other data from the literature,[1] seem to justify the assumption that no one electroencephalographic pattern is necessarily associated with coma and that no established relationships exist between the intensity of coma and the recorded cerebral-electrical activity.

Electroencephalographic responses to sensory stimuli have been observed in 2 of the 5 patients. Both were in deep coma. Electroencephalographic reactivity, in agreement with

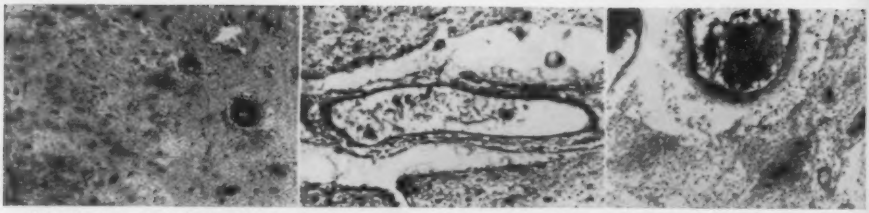


Fig. 8. (Case 5.) *Left*: Hemorrhagic infarction in the right hippocampus. *Center*: Perivascular infiltration. *Right*: Thrombosis in the basal meninges. Hemalum hematoxylin and eosin × 80

previous observations in comatose patients,[1] seems to correlate with the type of the electroencephalographic record, whether normal or slightly altered, but is independent of the intensity of coma.

In conclusion, it seems possible to state that the type of electroencephalographic activity, as well as the electroencephalographic reactivity to sensory stimuli, cannot be utilized for diagnostic and/or prognostic purposes in comatose patients. Finally, we would emphasize the apparently paradoxic finding that a normal or borderline electroencephalographic record with good reactivity may be present in a comatose patient some time before death.

The mechanism involved in determining the normal or borderline electroencephalographic activity in our 5 deeply comatose patients is not immediately apparent. Nevertheless, the relationship between our findings and those obtained in neurophysiologic investigations is of interest and importance. Experimental investigations carried out chiefly on cats and monkeys have shown that a large lesion, or

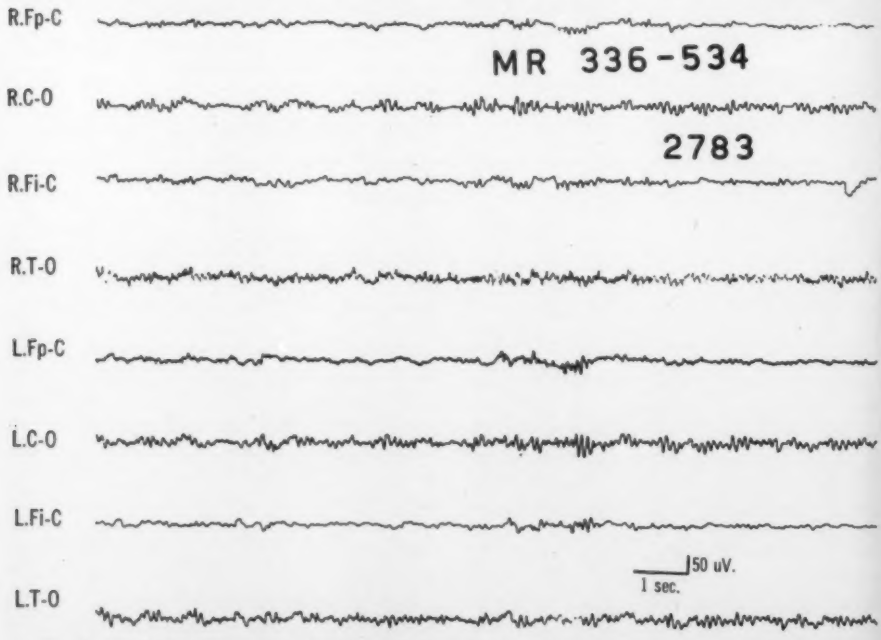


Fig. 9. (Case 5.) Electroencephalogram taken three days after the onset of coma (C3) shows a rather regular activity at 8 to 9 c/s, 30 to 40 microvolts in amplitude.

even an incomplete interruption in the pons, is at too caudal a level to affect significantly the electrocortical activity, which, therefore, maintains a normal appearance in spite of the decerebrate-like attitude of the animal.[12,13]. Accordingly, Gastaut[4] and Orthner[14] point out that lesions of the medulla oblongata and the pons in man modify neither the cerebral electrical activity nor the state of consciousness.

More detailed research has been recently carried out by Batini and others[15] on chronic preparations. The most important findings obtained by these authors are that, in cats, not only are electroencephalographic slow rhythms not produced until a complete transection of the brain stem reaches at least the pontomesencephalic junction but that a transection performed at the level of the middle pons just rostral to the trigeminal rootlets (midpontine pretrigeminal preparation) is followed by an enduring, low-voltage, fast activity which, in normal animals, is generally observed during states of wakefulness or alertness.

Although we are fully aware of the danger of transferring to the clinical field data and conclusions obtained in animals, even under chronic conditions, we think it is worthwhile to stress the analogy between the neurophysiologic findings just reported and Cases 3 and 4, who had large pontine lesions.

A more difficult task is to determine the possible mechanisms underlying the electroencephalographic pattern in the 3 other patients.

One might suggest that, in Cases 1 and 2, the indirect effects of the lesion (intracranial pressure, compression of the neighboring structures, and so on) could have produced an irritative effect[3] upon the brain stem. Although such hypothetical irritation could explain (according to the well-known experimental findings of Moruzzi and Magoun[16]) the low-voltage fast activity recorded, and although an explanatory hypothesis like this has already been advanced in similar cases,[4,17] it remains only a working hypothesis.

At this point, we wish to emphasize that electroencephalographic records of our 5 comatose patients were made from four to twenty-four hours before death. In this way, our cases recall the observation reported by Radermecker,[7] as well as the assertion made by Mathis, Torrubia, and Fischgold,[6] that "Meme la fréquence alpha existe dans le coma; sans topographie occipitopariétale et sans réaction d'arret, on la voit coexister avec suspension totale de la conscience vingtquatre heures avant la mort."

This statement, however, does not apply to our Cases 3 and 4, in which the reactivity to sensory stimuli was present, but does indicate that, in some patients (Case 5), the site and type of the lesions alone seem inadequate to explain the electroencephalographic features and other factors must be considered.

In fact, several works, both in animals[18–20] and humans,[17,21] show that circulatory and respiratory variations, changes in the blood pCO_2 or pO_2, and several other humoral alterations modify the electroencephalogram in different ways.

It is well known, for instance, that an increase in CO_2 content in blood circulating in the brain produces an increased fast activity; similarly, exceedingly high concentration of glucose, or high O_2 tension, produces an increased fast activity. On the other hand, variations in the internal environment, due, for instance, to hyper- or hypoventilation, to modification of blood glucose level, or to hyperthermia, frequently occur during deep coma, especially when death approaches.

Our data, therefore, suggest that there are probably 2 classes of patients who show normal or borderline electroencephalographic activity in coma. To the first class belong some patients with lesions located in the brain stem and with lesions associated with normal electroencephalogram and good reactivity. The second class includes some patients in whom electroencephalographic records are made some hours before death, when reversion of an abnormal electroencephalogram to a completely normal one, or to a record closely resembling the normal—even if reactivity is absent—seems possible.

Therefore, we suggest tentatively that the site of the lesion and/or the general variations of the internal environment account for the normal electroencephalographic activity in our patients.

On the contrary, no data are offered to explain how deep coma may be associated with

an electroencephalographic record containing no organized delta activity.

The current assumption that the same structures—the ascending reticular activating system—may be responsible both for the regulation of electroencephalographic activity and for the modification of the state of consciousness appears untenable in such pathologic cases.

Finally, one may arrive at the conclusion that the nervous structures involved in the regulation of the electroencephalographic activity and in the mechanism which gives rise to the state of consciousness are different or that these structures have different functional activities, so that the state of consciousness may be lost, while the electroencephalogram may or may not be modified.

Whatever the physiologic mechanism involved may be, we wish to emphasize the fact that there not infrequently are changes in the nature of the electroencephalogram and in the state of consciousness which are completely independent of one another and which can not be linked directly to a common mechanism. This fact should be stressed, not only for its practical clinical implication, but also because of its importance for neurophysiologic concepts.

SUMMARY

A clinical, electroencephalographic, and anatomic study was made of 5 patients in deep coma.

Normal or borderline electroencephalographic activity, as well as a good reactivity to sensory stimuli, may be associated with deep coma. The types of electroencephalographic activity and reactivity have no diagnostic or prognostic significance.

The site of the lesions and/or the variations of the internal environment may account for the unusual pattern of electroencephalographic activity.

The assumption seems untenable that the same nervous structures are involved in the regulation both of electroencephalographic activity and of mechanisms which give rise to the state of consciousness.

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Effect of air embolism on permeability of cerebral blood vessels

J. C. Lee, M.D., M.Sc., and J. Olszewski, M.D., Ph.D.

INJECTIONS OF AIR into the carotid artery of the cat produce a considerable increase in cerebral vascular permeability, as is well known.[1] This increase is of such magnitude that even particles the size of albumin can pass through blood vessel walls and enter the nervous parenchyma. The experiments reported here were conducted in order to study (1) how long the heterologous albumin which penetrated the nervous tissue as a result of air embolism will remain there; and (2) whether there are any species differences in susceptibility to vascular damage by air embolism.

MATERIAL AND METHODS

A total of 18 cats and 7 rabbits of both sexes, ranging from 0.9 to 2.8 kg., were used. Anesthesia was induced by injecting 0.5 cc. of Nembutal per kilogram of body weight into the liver of the cat and into the auricular vein of the rabbit.

Radioactive iodinated bovine albumin was used as an indicator of permeability changes. It was obtained commercially from C. Frosst & Co. of Montreal. According to the manufacturer, the concentration of albumin in the solution is 2% and not more than 2% of the radiation is due to unbound I^{131}. Iodination was performed by a modification of the method of Gilmore and associates.[2] From 3.5 to 5 cc. of the solution was injected intravenously, either before or after air embolism. Strength of radioactivity was approximately ½ mc. per kilogram of body weight. In 3 experiments on rabbits, trypan blue instead of tagged albumin was used to test permeability changes. For this purpose, 70 cc. of 0.5% trypan blue in saline was injected intravenously.

To produce air embolism, the left common carotid artery was exposed and injected with 0.2 cc. of air. After five minutes, the injection was repeated using the same amount of air. Dosage of air was reduced to 0.1 cc. per injection for animals weighting 1 kg. or less. In some experiments, a single injection of 0.2 or 0.4 cc. of air was given. The results were the same as in those given 2 injections.

At a predetermined time after the injection of tagged albumin, the animals were killed by perfusion with 6% dextran. The exchange perfusion and preparation of autoradiographs have previously been described in detail.[3]

RESULTS

As anticipated, the experiments showed that healthy cerebral blood vessels are impermeable to heterologous bovine albumin and also to trypan blue. No radioactivity or blue staining of normal brain tissues was observed, except for the choroid plexus, neurohypophysis, and tuber cinereum (the eminentia saccularis, Wislocki and King[4]), which were slightly radioactive or discolored blue in every case.

Cats. Experiments were performed on 13 cats to determine how long the brain remained radioactive after iodinated albumin entered the nervous tissue as a result of air embolism. In anesthetized cats, the air embolism was induced as described above and the albumin was injected intravenously immediately thereafter. The animals were killed from one-half to twenty-four hours later. The results are shown in the table. With the exception of experiment 151, no pathologic changes were observed.

As can be seen from the table and accompanying figures, the radioactivity was small after the first half hour, but rapidly increased

From the Laboratory of Experimental Neuropathology, Department of Pathology, University of Saskatchewan, Saskatoon.

This work was supported by a grant from the National Research Council of Canada.

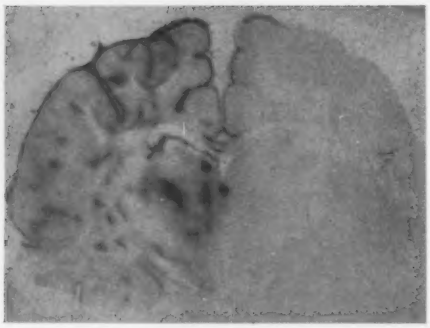

Fig. 1 (Exp. 158). Autoradiograph of a coronal section of the brain of a cat killed one-half hour after air embolism on the left side. A moderate degree of radioactivity is confined to the left cerebral hemisphere. Note that the patchy radioactivity is distributed in the gray matter, while the white matter is only faintly radioactive.

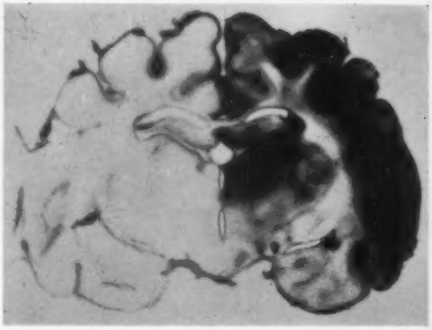

Fig. 2 (Exp. 142). Autoradiograph of a coronal section of the brain of a cat killed one hour after air embolism. The radioactivity is very intense but is present in the same areas as those of Figure 1, being most pronounced in the cerebral cortex of the frontoparietal region and in the dorsal region of the thalamus. The white matter adjacent to the cortex is faintly radioactive. (The sides in this figure are reversed.)

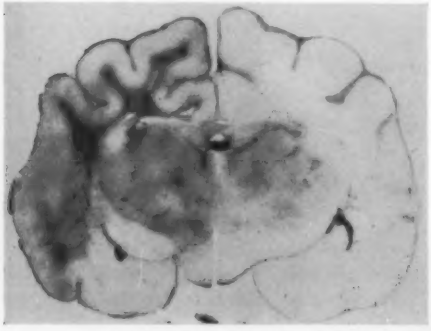

Fig. 3 (Exp. 406). Autoradiograph of a coronal section of the brain of a cat killed four hours after air embolism. Moderate radioactivity is observed in the left cerebral cortex, corpus striatum, and thalamus. The opposite thalamus is also radioactive. Note that certain regions of the subcortical white matter are more radioactive than the adjacent cerebral cortex.

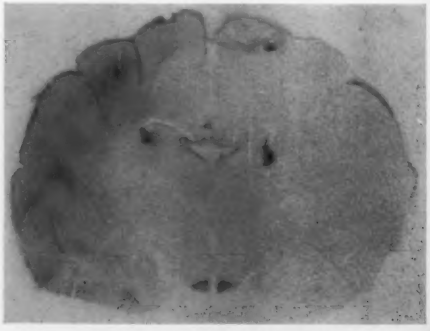

Fig. 4 (Exp. 156). Autoradiograph of a coronal section of the brain of a cat killed six hours after air embolism. Moderate radioactivity is present in the lateral aspect of the left cerebral cortex. The thalamus and corpus striatum are only faintly radioactive.

during the next, reaching its maximum one hour after air embolism. From this time on, it began to decrease quite rapidly, becoming slight after four to six hours, and almost completely disappeared at twenty-four hours. In general, the radioactivity in the gray matter was more pronounced than in the white matter. However, in four experiments, some regions of the subcortical white matter were more radioactive than the overlying cortex.

In experiment 151, the nerve cells at the bottom of certain sulci of both cerebral hemispheres lost their stainability by Nissl's method. With hematoxylin-eosin stain, these cells appeared shrunken and surrounded by round spaces. A moderate proliferation of the microglia was also present (Figs. 5 and 6). In other regions of the cortex, the stainability and normal characteristics of the nervous tissue were well preserved.

For reasons which will be discussed later, 3 experiments were done on cats to determine how long the effects of air embolism on cerebral vascular permeability to iodinated albumin would last. The animals were injected with tagged albumin at periods of one-half (experiment 411), one (experiment 412), and two hours (experiment 149) after embolization. One hour after the injection of albumin, they were killed. In experiment 411, autoradiographs showed intense radioactivity over the dorsal aspect of the left cerebral cortex and the dorsal areas of the left thalamus. Moderate darkening also was observed in the opposite

Experiment number	*Air injection*	*Survival time in hours*	*Permeability changes observed in autoradiographs*	*Remarks*
158	double	½	Moderate patchy radioactivity confined to the left cerebral cortex, thalamus, and corpus striatum. Faint radioactivity in the white matter (Fig. 1)	
407	single	½	Ditto	
142	double	1	Intense radioactivity in the left cerebral cortex of the frontoparietal region and the dorsal area of the thalamus. Moderate radioactivity in the left corpus striatum, hippocampus, and subcortical white matter (Fig. 2)	
159	double	1	Ditto	
421	single	2	Radioactivity in the same areas as those of experiment 142 but less intense	
160	double	4	Moderate radioactivity confined to the left cerebral cortex, thalamus, and corpus striatum. The subcortical white matter slightly radioactive	Certain regions of the subcortical white matter are more radioactive than the cortex.
406	single	4	Ditto	Certain regions of the subcortical white matter are more radioactive than the cortex. Moderate radioactivity in the opposite thalamus (Fig. 3)
156	double	6	Moderate radioactivity in the left cerebral cortex. The thalamus and corpus striatum only faintly radioactive (Fig. 4)	
410	single	8	Radioactivity in the same areas as experiment 156. In addition, slight radioactivity in the opposite thalamus	Certain regions of the subcortical white matter are more radioactive than the cortex.
151	double	14	Faint radioactivity in the dorsolateral regions of the left cerebral cortex	Nerve cells of some areas lost stainability by the Nissl method (Figs. 5 and 6).
409	single	16	Faint radioactivity in the left cerebral cortex and thalamus	The white matter is slightly more radioactive than the overlying cortex.
153	double	24	Faint radioactivity, barely visible, in the left cerebral cortex. No radioactivity in the thalamus (Fig. 7)	
408	single	24	Ditto	Certain regions of the subcortical white matter are more radioactive than the cortex.

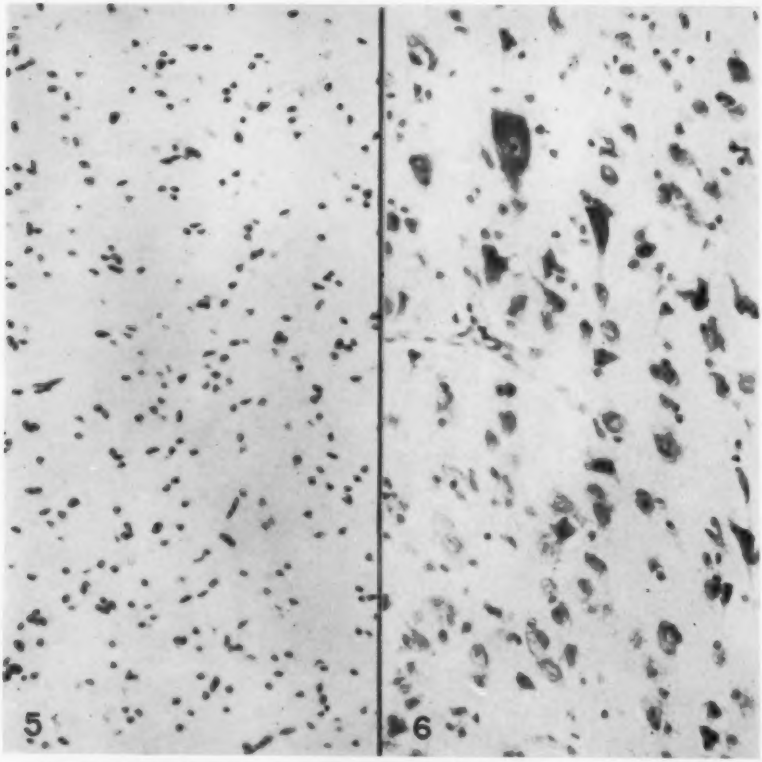

Fig. 5 (Exp. 151). Photomicrograph taken from the brain of a cat killed fourteen hours after air embolism. It shows loss of stainability of the cortex at the depth of the sulcus. A moderate proliferation of microglia is seen. (Nissl stain, × 200)
Fig. 6 (Exp. 151). Photomicrograph taken from the same brain as that of Figure 5. It shows that nerve cells in the lateral wall of the same sulcus are stained normally. (Nissl stain, × 200)

Fig. 7 (Exp. 153). Autoradiograph of a coronal section of a cat killed twenty-four hours after air embolism. Minimal radioactivity is visible in the left cerebral cortex.

thalamus. The white matter of certain subcortical regions was more radioactive than the adjacent cortex (Fig. 8). In experiment 412, only faint radioactivity was seen over the free border of the left cerebral hemisphere (Fig. 9). In experiment 149, no radioactivity was observed in the brain except for the tuber cinereum and choroid plexus, which, as mentioned before, were radioactive in each case.

Rabbits. Experiments were carried out on

5 rabbits to test the effects of air embolism on the cerebral vascular permeability to iodinated albumin and to compare them with those obtained in cats.

Experiment 193. The rabbit was injected with tagged albumin immediately after air embolism and was killed one hour later. Autoradiographs showed no radioactivity in either the gray or white matter. Only a faint trace of darkening was observed in the tuber cinereum and choroid plexus.

Experiment 206. To ensure that the negative result obtained in experiment 193 was not due to any technical error, the experiment was carefully repeated on another rabbit. Both autoradiographs and histologic sections showed the same negative results as in experiment 193.

Since experiments 193 and 206 revealed that air embolism did not make the cerebral blood vessels of the rabbit permeable to iodinated albumin, trypan blue was used in 3 further experiments with rabbits. This was done to confirm that in our hands intracarotid air injection in rabbits actually did produce cerebral air embolism followed by permeability changes, as were to be expected from the experiments of Broman.[5] At the same time, we wanted to compare roughly the duration of increased permeability to trypan blue in rabbits with that to albumin in cats. Trypan blue was injected into 3 rabbits at various time intervals after air embolism. Each was killed by overdosage of Nembutal one hour after the injection of trypan blue. No exchange perfusion was carried out, but postmortem perfusion by normal saline followed by formal-alcohol (10% formalin in 30% alcohol) was performed.

Experiment 173. The rabbit was injected with trypan blue immediately after induced air embolism. Gross observation of the brain revealed that the left cerebral hemisphere, the side of air injection, was tinged blue except for the ventral surface of the temporal lobe. In coronal sections, the left cerebral cortex, thalamus, and corpus striatum were all similarly stained. The blue areas coincided with the radioactive areas observed in brains of cats after intracarotid injections of air. No microscopic sections were prepared in this experiment or in experiments 175 and 177.

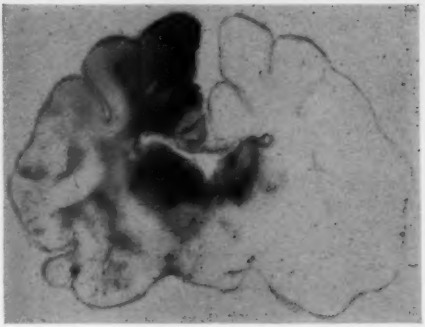

Fig. 8 (Exp. 411). Autoradiograph of a coronal section of the brain of a cat which was injected with labeled albumin one-half hour after air embolism and killed one hour later. Considerable radioactivity is present in the dorsal regions of the left cerebral cortex and thalamus. The opposite thalamus is also darkened. Note that certain areas of the white matter are more radioactive than the adjacent cortex.

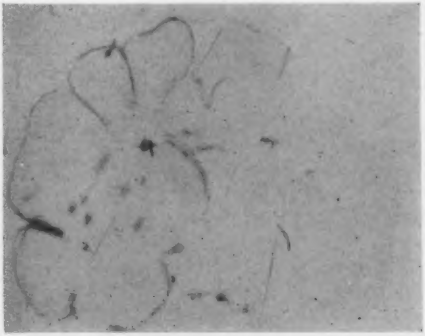

Fig. 9 (Exp. 412). Autoradiograph of a coronal section of the brain of a cat which was injected with labeled albumin one hour after air embolism and killed one hour later. A faint radioactivity is present over the free border of the left cerebral hemisphere and in a few small spots in the white matter.

Experiment 175. The rabbit was injected with trypan blue one hour after air embolism. The blue discoloration of the left cerebral hemisphere was less intense than in experiment 173. In coronal sections, the trypan blue stained the same areas of the brain as those of experiment 173.

Experiment 177. The rabbit was injected with trypan blue one and one-half hours after air embolism. The blue discoloration was very faint, but it also involved the same areas as those seen in experiment 173.

DISCUSSION AND CONCLUSION

1] In experiments to trace molecules which have been labeled with radioactive isotopes, an important consideration is the stability of the bond between these 2 substances. Iodinated albumin is considered to have a very stable nature, and the iodine is known to remain attached to the tyrosine even when the albumin is split into its constituent amino acids. Although it is possible that some of the observed radioactivity might be due to molecules smaller than total protein, it is unlikely to be due to ionic iodide, since the unbound iodide would be washed away during the perfusion and histologic procedures used in this study.

2] In conformity with observations by other authors, we have found that injections of air into the common carotid artery of cats and rabbits produce an increased permeability of the cerebral blood vessels in the corresponding hemisphere.[1,5] A slight extension into the opposite hemisphere can be explained by spread of air bubbles through the circle of Willis or, perhaps, through the anastomosing vessels in the massa intermedia of the thalamus. The most affected regions of the brain were the frontoparietal cortex and dorsal thalamic areas. This pattern of distribution corresponds to the territory supplied by ramifications of the anterior and middle cerebral arteries.

3] A rather surprising finding was the rapid disappearance of radioactivity from the brain after air embolization. The radioactivity reached a peak in about one hour and declined rapidly during the next four to six hours. After twenty-four hours, there was practically no radioactivity in the brain. The short duration of the increased permeability produced by air embolism could be a factor contributing to this phenomenon. During the period of increased permeability, the albumin enters the brain tissue and, though there can also be movement in the opposite direction, the net result is an accumulation because of the high concentration within the blood stream. However, this increase in permeability lasts only about one hour and after this no more albumin is added to the extravascular pool.

There are 3 possible explanations for the rapid decline of radioactivity in the brain tissue: [1] The albumin can be metabolized into smaller particles, which may easily pass back into the blood stream. [2] The albumin or its metabolites in the brain tissue may enter the cerebrospinal fluid, from whence they can be reabsorbed into the blood circulation. [3] The intact molecules of albumin may be able to reenter the blood vessels from the brain tissue. It is felt that the last possibility is rather remote, since it would necessitate a different order of permeability from the blood to the brain than that from the brain to the blood. It is more likely that the first 2 processes are present simultaneously, though it is difficult to say which is more important. The investigations of Bakay[6] and our own unpublished data indicate that the brain and cerebrospinal fluid are "in equilibrium" and that the passage of substances, at least from the cerebrospinal fluid into the brain, occurs very easily. We can assume, therefore, that a significant proportion of radioactivity disappears via the cerebrospinal fluid.

4] An unexpected and interesting finding was the absence of increased cerebrovascular permeability to albumin molecules in the rabbit after air embolism, while permeability to trypan blue was enhanced by this procedure. Thus, these experiments demonstrated that the permeability, though increased for one substance, may still remain unchanged for another. The difference in molecular size between trypan blue and albumin is the simplest explanation for this phenomenon. However, other more subtle differences in the properties of different substances also may be responsible for the varying ease with which they penetrate the brain tissue under normal and pathologic conditions. In addition, it is apparent from these experiments that the alteration in vascular permeability may vary from species to species, even if the same noxious agent is used. The cause of this variation cannot at present be satisfactorily explained. Perhaps there are differences in the hemodynamics of the cerebral circulation or alter-

nately significant differences in the property of the blood-brain barrier between the cat and the rabbit.

5] As has been observed by Broman,[5] the increased permeability of the cerebral vessels resulting from air embolism is very transient. He observed that the vascular impermeability to trypan blue was restored approximately one hour after embolization. In our experiments, the same results were obtained using iodinated albumin. The number of our experiments was too small to establish an accurate comparision of the length of permeability increase between the cat and rabbit as related to albumin and trypan blue. However, the values are of approximately the same order, about two hours.

6] With the exception of experiment 151, no histopathologic changes were observed in our material. This indicates that increased permeability may be present without histologic changes, as seen under an ordinary light microscope. This substantiates Klatzo's[7] findings that the increased vascular permeability precedes the appearance of edema by approximately twelve hours.

The interpretation of pathologic changes in experiment 151 is rather difficult. Since they are present bilaterally, it is unlikely that they result from unilatral air embolism. In addition, no such changes were seen in the other animals. This type of lesion indicates a generalized injury such as observed, for instance, in hypoxia. However, nothing unusual was observed in the behavior of this animal during recovery from the anesthesia or in the subsequent period. It is interesting to note that the lesions are present in the depth of sulci and, thus, their distribution is similar to neuronal loss and gliosis in cases of infantile paraplegia and in various anoxic conditions.

7] In several animals, the subcortical white matter was more radioactive than the gray matter. This was particularly pronounced in animals which were killed a few hours after the air embolism. This phenomenon perhaps can be correlated with the greater susceptibility of the white matter to edema. The absence of microscopic evidence of edema may be due to the short periods between the air embolism and the death of the animals.

SUMMARY

1] The healthy cerebral blood vessels of the cat and rabbit are not permeable to radioactive iodinated bovine albumin and trypan blue.

2] Air embolism renders the cerebral blood vessels of the cat permeable to albumin molecules. This increased permeability is confined to the areas supplied by branches of the left carotid artery, through which the air was injected.

3] The radioactivity of the brain tissue after embolization is of a comparatively short duration. It reaches a maximum in the first hour, declines quickly in the next four hours, and disappears almost completely at the end of twenty-four hours.

4] The duration of the effect of air embolism on cerebrovascular permeability is very transient. In cats, no radioactivity was seen in cerebral autoradiographs when labeled albumin was injected two hours after embolization. In rabbits, only a faint blue color was observed in the brain when trypan blue was injected one and one-half hours after embolization.

5] There is a species difference in the response of cerebral blood vessels to a noxious agent. In addition, in the same species, a given noxious agent can increase the permeability to one test substance but not to the other.

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Neurology

BOOK REVIEWS

Pathogenesis and Treatment of Parkinsonism

edited by William S. Fields, 372 pp., ill., Charles C Thomas Co., Springfield, Ill., 1958. $10.50.

This book, the most recent of a series of transcripts of the annual symposia sponsored by the Houston Neurological Society, shares with its companion volumes the interest of dealing with a lively subject in a lively way.

The main topics considered by the 24 contributors are the antomic and physiologic basis of tremor and other involuntary movements, epidemiology, the pathology of parkinsonism, the medical treatment of Parkinson's disease including physical therapy, and surgical procedures designed to relieve or abolish tremor and rigidity.

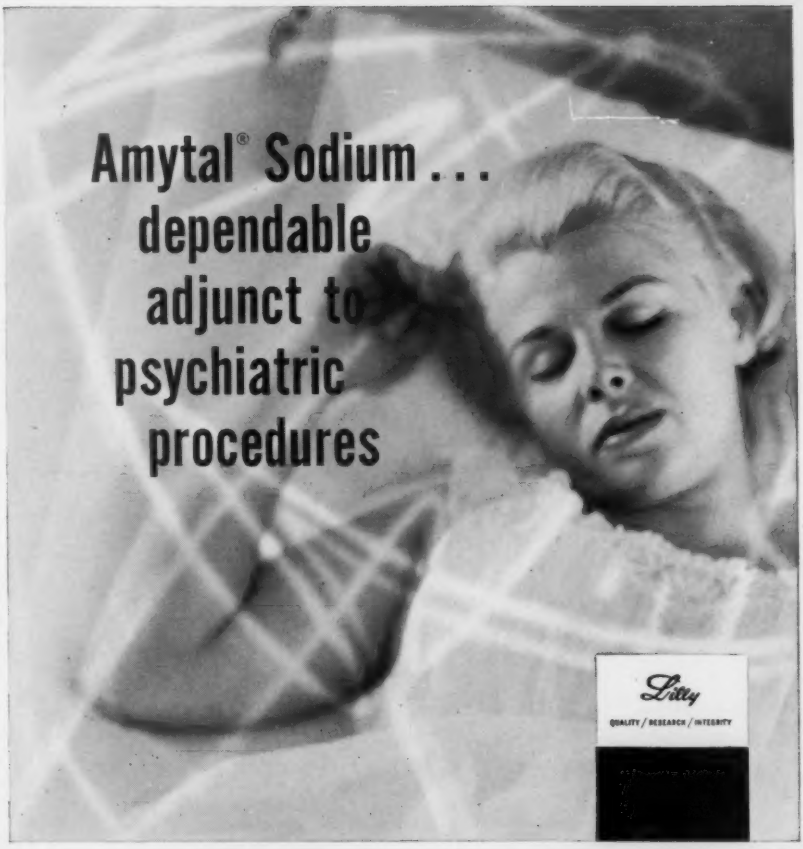
It is impossible to summarize in a short review such a wide range of information and viewpoints and even biases of so many. Fortunately, at the end of the volume, A. E. Walker presents a balanced statement of the salient problems developed by the symposium, giving cohesion to an effort which is, of necessity, something of a patchwork. However, this book contains the gist of current thinking in the United States on the pathogenesis and treatment of Parkinson's syndrome.

As would be expected, the main focus of interest is upon the now very considerable body of new information that has accumulated—especially during the past five years—from the attempts of neurosurgeons to influence tremor and rigidity by controlled destruction of selected portions of the basal ganglia and other deep-brain structures. Important and hopeful as these new observations are, it is clear that they remain in a largely undigested state. Many questions crucial for their therapeutic application are far from solved. It is not known, for instance, precisely where the destructive lesions must be placed or how extensive the lesions must be in order to be effective.

One important reason for the uncertainty and for the differences of opinion on this point is simply that adequate anatomic controls of successful and unsuccessful cases are not available, except in a few instances. Too often, the surgeon's intent is taken for the deed, a violation of one of the first principles of neurophysiologic investigation. Equally perplexing for the clinical neurologist is the lack of agreement on the question of the proper choice of patients and the indications for surgical procedures of this type.

The reviewer would like to take this opportunity to complain about the increasing carelessness in proofreading which has crept into medical publication in this country in recent years. Not only are the typographic errors in this book so numerous as to be a real blemish, but also many are of a kind that confuse and distort the meaning of the text—which is even more intolerable.

R. B. R.



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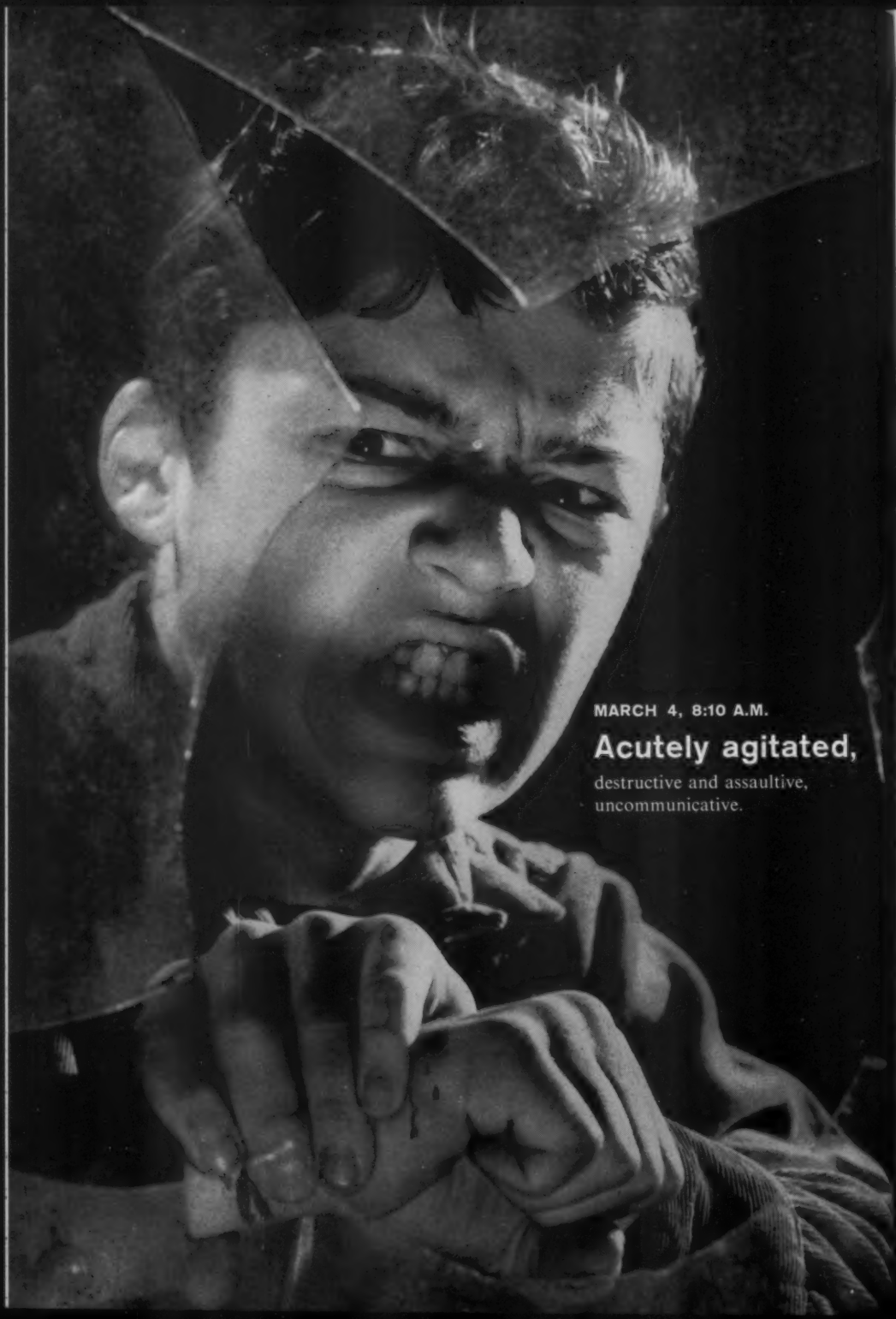
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Acutely agitated,
destructive and assaultive,
uncommunicative.

RCH 4, 10:00 A.M.
ARINE, I.V., has been given.
ient in light sleep.
n be awakened readily,
d responds to questioning.

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about smashed window.

MARCH 8, 9:00 A.M.
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CHEMICAL ADVANCES IN THE STUDY OF THE MIND

Psychic energizers and synthetic hallucinogens recently attracted wide-spread interest at a conference entitled, A Pharmacologic Approach to the Study of the Mind, held early this year.

Psychic energizers inhibit enzymes that destroy neurohormones in the brain and other body tissues. Neurohormones influence blood pressure, emotions, and other functions beyond conscious control.

Dr. Nathan Kline of Rockland State Hospital, Orangeburg, N. Y., described the effectiveness of the agents in the commonest psychiatric disturbance—depression. Dr. Kline pointed out that administration of psychic energizers is just as effective as shock treatment, besides being safer, more convenient, less expensive, and greatly preferred by patients. In addition, Dr. Kline states that they provide pharmacologic evidence of what may be the basic chemical pathology in some cases of depression, whereas electroshock is a nonphysiologic treatment, the mode of action of which is poorly understood.

Catron, a psychic energizer about 10 times more powerful than iproniazid (Marsilid), given to 400 patients was found to be a potent antidepressant agent that relieves many types of depression. The drug acts rapidly, sometimes within a few weeks, and is relatively safe.

Based on a study of 123 emotionally disturbed children, Dr. M. A. Perlstein of Northwestern University, Chicago, stated that Catron might be effective in 70 to 75% of cases, with proper screening procedures.

The drug was reported to relieve pain in such conditions as cardiac angina. Dr. Henry Agin of Beth El Hospital, Brooklyn, N. Y., using subclinical doses in nondepressed patients receiving psychotherapy, reported that patients became more alert, responsive, and more eager to continue treatment within ten days. Catron is a product of Lakeside Laboratories, Milwaukee, Wis.

Hallucinogens are agents capable of inducing model psychoses; treated persons lose contact with reality and have visual and auditory hallucinations for a limited period of time. Dr. Lee Abood of the University of Illinois, Chicago, reported encouraging results in psychotic patients given hallucinogen antagonists.

Ditran, a synthetic hallucinogen not yet commercially available, has a far more powerful effect than mescaline or lysergic acid, finds Dr. Abood. Used to induce a model psychosis, Ditran is a powerful tool for studying the mechanism of drug action on the mind, said Dr. Abood. He noted that Ditran had also been used successfully in the treatment of depression.

(Continued on page 27A)

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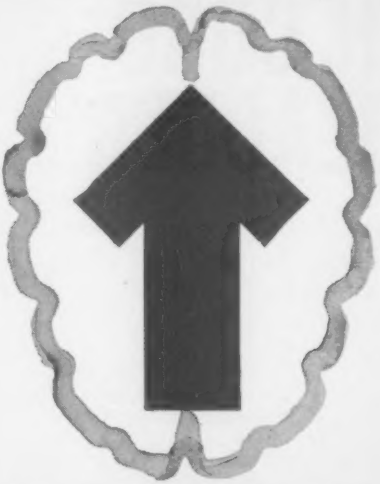
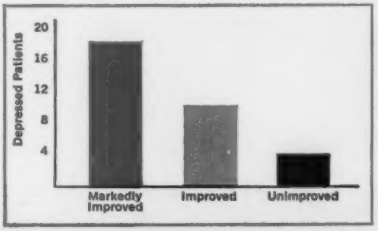


Revitalizes depressed patients—elevates mood, increases alertness and ability to maintain work and social adjustment.[1,2]



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*W.A. Leff, *Antibiotic Med. & Clin. Therapy*, 6: (Suppl. 1), 44-48, Feb. 1959.

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(Continued from page 25A)

CEREBRAL ANGIOGRAPHIC DIAGNOSIS OF STROKES

Cerebral angiography, an x-ray diagnostic technic that provides accurate and precise factual information on the cause of brain strokes, is revolutionizing the management of cerebrovascular disease, says Dr. Robert A. Kuhn, of St. Clare's Hospital, Denville, N. J. Since the development of the opaque medium, diatrizide sodium (Hypaque) by Winthrop Laboratories, New York City, the procedure, previously carrying some risk to the patient, is both highly effective and safe. Injection of 30 cc. of a 50% Hypaque solution provides visualization of two-thirds of the brain's arterial and venous circulation and the entire circulation of the blood in the neck on the way to the brain.

The usual stroke develops because of interference with blood supply to the brain, usually due to arterial disease. Dr. Kuhn states that plugging of the carotid artery in the neck accounts for as many as one-fourth of strokes. The frequency with which this type of stroke is being diagnosed is attributable to the increasing use of cerebral angiographic examination.

SKELETAL MUSCLE RELAXANT

Robaxin Injectable is particularly designed and recommended for prompt relief of the acute phase of skeletal muscle spasm. Effects are usually seen within ten minutes after intravenous or intramuscular administration. The oral form of Robaxin may be used for maintenance doses. Ampules contain 1 gm. of methocarbamol in a 10-cc., sterile, 50% solution of polyethelene glycol-300. Tablets contain 0.5 gm. of methocarbamol. The drug is manufactured by A. H. Robins Company, Richmond, Va.

PROMOTION OF WEIGHT LOSS WITHOUT JITTERS

Administration of Levonor helps overweight patients stick to their low calorie diets without causing nervous stimulation or insomnia. Levonor, a prescription drug, was developed by Nordson Pharmaceutical Laboratories, Irvington, New Jersey.

In a double-blind study, Levonor was given to 12 and placebos to 12 persons on a daily 1,000 calorie diet. Average weekly weight reduction in Levonor-treated persons was 2.5 lb., Dr. Feldman says. Of the patients receiving placebos, 8 lost less than a pound a week and 4 gained weight. Levonor, being an appetite suppressant, made it possible for patients to stay on their diets.

In another study, 45 over weight men and women ranging in age from 15 to 61 years were placed on low-calorie diets and given 2 or 3 Levonor tablets a day. Weight loss averaged 2.4 lb. per week. Dr. Feldman noted that none of the patients complained of insomnia. This is particularly striking in view of the fact that some took the drug as late as 8 or 9 P.M.

new psychoactive agent

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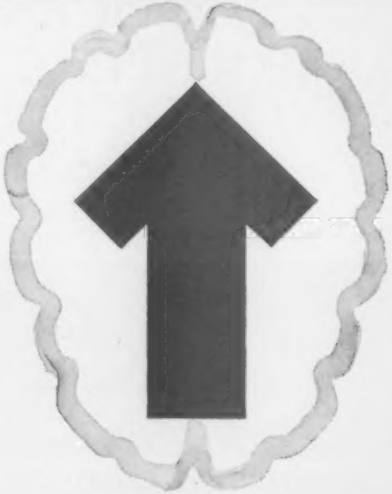
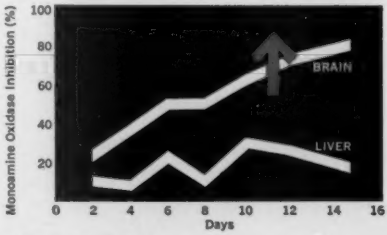


Brightens mood, dispels apathy, melancholy, social withdrawal through selective suppression of monoamine oxidase (MAO) of brain at doses which have little or no effect on liver.



Horita, A.: Report, Mar. 17, 1958

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TINY TABLET UNDER TONGUE
STOPS MIGRAINE
'SICK' RECURRENT HEADACHE
FAST
SHUTS OFF PAIN
BLOCKS OUT FEAR
ANYTIME, ANYWHERE, WITHOUT NEED EVEN FOR A GLASS OF WATER

because prodromal warning usually tells patients that the time to arrest imminent migraine attack is right now, and the place to do it is right here.

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SUBLINGUAL ERGOTAMINE TARTRATE TABLETS

MORE CONVENIENT... NO WATER, INJECTIONS OR PRIVACY NEEDED

All the patient has to do is to place a tiny ERGOMAR tablet under tongue. It enters blood stream directly through buccal lining, bypasses stomach and hepatic system and aborts vascular headache and migraine in approximately one half the usual time of ingested tablets.[1-5]

Dosage: Sublingually, 1 tablet at onset of attack. Additional doses may be taken, if necessary, as follows: 1 tablet every half-hour until relief is obtained. Total dosage must not exceed 3 tablets within 24 hours.

Contraindications: Peripheral vascular and coronary heart disease, hypertension, renal or hepatic dysfunction and pregnancy.

Supplied: ERGOMAR Tablets, 2 mg. ergotamine tartrate per tablet, in specially developed dispenser packages of 12 tablets. *May we suggest for patient convenience and economy, writing for not less than 12 tablets in a prescription.*

References: 1. DeJong, R. N.: GP *19*:147, 1959. 2. Scientific Exhibit, 9th Annual Meeting, Am. Acad. Neurology, Boston, Mass., April 22-27, 1957. 3. Berman, B. A.: Current personal communication in the files of Nordson Laboratories. 4. Saunders, S. H.: Current personal communication in the files of Nordson Laboratories. 5. Blumenthal, L. S., and Fuchs, M.: Am. Acad. Neurology, Los Angeles, Calif., April 15-18, 1959. *Sublingual Administration of Ergotamine in Relief of Migraine and Vascular Headache.*

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*PAT. PENDING

CORRESPONDENCE

TO THE EDITORS: In the April 1959 issue of *Neurology* (p. 256), White and Wheelan report the results of an epidemiologic study of multiple sclerosis in the Kingston, Ontario, region. They conclude that variations in the geographic incidence of multiple sclerosis do not occur in this area. In their discussion, they attempt to evaluate critically other similar studies. There can be no doubt that such criticism and reevaluation are desirable and necessary. However, when the criticism is based on misinterpretation, this should be called to the attention of the reader.

On page 268 they state that "Swank studied cases in Norway and reported a higher incidence around areas of the densest population." They supported this statement by two maps of Norway; one similar to a map in our paper showing the incidence of multiple sclerosis in different parts of rural Norway (Fig. 4) and a second map of their own (Fig. 6) showing the areas of densest population in Norway. Examination of these maps shows that the areas of densest population in Norway are often areas of low incidence of multiple sclerosis rather than high. Except immediately around Oslo and Trondheim, the population is most dense along the coast. This corresponds in the main to the area of low incidence of multiple sclerosis. The population is least dense in the central part of Norway. This often corresponds to the areas of high and very high incidence of multiple sclerosis. Table 3 in our paper shows that the multiple sclerosis incidence in the sparsely settled inland area is almost 4 times the incidence of multiple sclerosis observed along the more thickly populated coast.

To establish this point, we have measured the relative square centimeter areas of the high and low incidence areas on the map of Norway reproduced in our paper with a planimeter. The northern part of Norway, including Finmark, Troms, and Nordland, have been analyzed separately from the rest of Norway south of this area. The results are contained in the table. In the north zone, the area of high incidence of multiple sclerosis has a slightly greater density of population (number

(Continued on page 30A)

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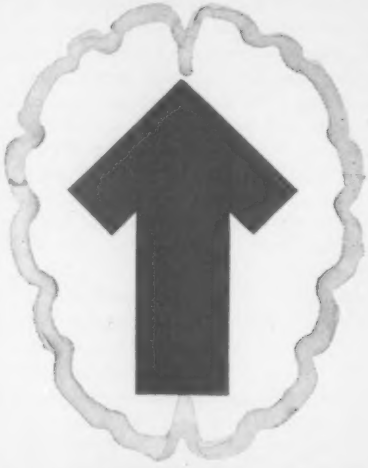
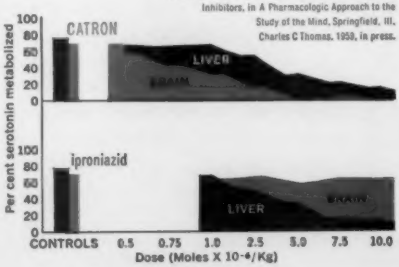


Elevates mood, brightens outlook by raising levels of mood-controlling neurohormones, serotonin and norepinephrine . . . at doses which have little or no effect on the liver.

Norita, A.: The Pharmacology of the Monoamine Oxidase Inhibitors, in A Pharmacologic Approach to the Study of the Mind, Springfield, Ill. Charles C Thomas, 1959, in press.



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of people per square centimeter on map) than the area of low incidence of multiple sclerosis. In the south, the area of low incidence of disease has the greater density of population. Further, the area of low incidence of multiple sclerosis in the south has a population density more than double the population density of the area of high incidence of multiple sclerosis in the north. The rural population is relatively dense in Akerhus near Oslo and here the incidence of multiple sclerosis is moderately high. However, as one goes inland in Akerhus the rate rises. The incidence often becomes higher in the most inaccessible and least populated mountainous parts of Norway as shown in Figure 1 of our paper (*New England J. Med.* 246:721, 1952). It is clear that the incidence of multiple sclerosis in Norway is not determined by the density of the population. In general, however, the area of high incidence of multiple sclerosis corresponded to the area of low density of population.

White and Wheelan also conclude that the area of high incidence of multiple sclerosis in Norway corresponds to areas which by virtue of transportation facilities would make it easy for the patients to get to diagnostic centers. Here again we disagree. Their map (Fig. 5), purporting to support this statement, shows rail and road facilities incompletely when compared with rail and road maps published by the Norwegian Government at the end of World War II. Even so, it is clear that, in the Oslo and Oslo fjord area, the road and rail system is most complete near the coast where the incidence of multiple sclerosis is not as high as in some other areas. Inland transportation facilities are relatively sparse, and the incidence of multiple sclerosis is either high or very high. On the west coast of Norway, both rail and road transportations are poor. Also the incidence of multiple sclerosis is very low. Travel in this part of Norway is effectively accomplished by boat. This is also the cheapest and the traditional method of travel in this part of Norway. Diagnostic centers are relatively numerous and accessible in these areas of low incidence of multiple sclerosis, in Trondheim, Kristiansand, Bergen, Stavanger, and so on.

During the period of our survey (1935-48), medical care in clinics throughout Norway was free to all who needed or wanted it. Further, in addition to the District doctor and the Provincial doctor, the District nurse visited every family twice a year, more often when indicated. People who needed medical care were sent to the nearest diagnostic hospital when the visiting nurse (or doctor) felt this was indicated. Here they were evaluated by neurologists or, if necessary, they were sent to Oslo to the clinic of Professor Monrad-Krohn. White and Wheelan make much of the fact that we failed to obtain information from some neurologists in private practice. Our epidemiologic data showed that practically all patients seen by neurologists privately were also studied at state hospitals which were our main source of data.

A minor misquotation is their reference number 10. In this paper, we suggest that fat intake may be related to the incidence of multiple sclerosis but do not report cases treated with low-fat diet. The authors were probably referring to a later paper in which eight years' experience in treatment of multiple sclerosis with low fat diet was reported (*Ann. Int. Med.* 45:812, 1956).

I wish to thank White and Wheelan for calling attention to our paper which I feel merits serious consideration in the search for the cause and treatment of multiple sclerosis.

ROY L. SWANK, M.D.
University of Oregon, Portland

	Relative incidence of multiple sclerosis	*Per cent of total land area*	*Rural population*	*Area in square centimeters*	*Population per square centimeter on map*
North zone (Finmark, Troms, and Nordland)	High	4%	16,800	0.4	42,000
	Low	96%	315,663	9.5	33,227
South zone (Rest of Norway)	High	63.8%	1,123,026	12.2	92,051
	Low	36.2%	791,691	6.9	114,737

withdrawn apathetic rejected gloomy
remorseful hopeless listless despairing
forlorn somber defeated
bitter crushed

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MEAN DEPRESSION,
THE TREATMENT IS

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How to use this new drug:

CATRON Hydrochloride is a monoamine oxidase (MAO) inhibitor useful in the treatment of depression and of other disorders indicated below. It is recommended for use in carefully selected cases and in those patients who have not responded to the milder drugs.

ADMINISTRATION AND DOSAGE

Dosage of CATRON must be individualized according to each patient's response. The initial daily dose should not exceed 12 mg. and should be reduced as soon as the desired clinical effect is obtained. In severe depressions some clinicians desire rapid results and begin treatment with 24 mg. daily: this dosage should not be continued for more than a few days. A single daily dose in the morning is recommended. A continuous or interrupted schedule may be used, the latter during the maintenance period.

DEPRESSION (Endogenous, Reactive, Postpartum, Involutional and Depression Secondary to Schizophrenic or Neurotic Reaction): initially, 12 mg. once daily for approximately 2 weeks, or less if improvement appears. Dosage is then reduced to 6 mg. daily. As improvement continues, maintenance dosage of 6 mg. every other day or of 3 mg. daily often proves satisfactory. An interrupted dose schedule is recommended for long-term therapy.

ANGINA PECTORIS—3 to 6 mg. daily in most cases. Relief of pain and elevation of mood may be dramatic. Victims of angina pectoris who respond in this manner should be cautioned against overexertion induced by their sense of well-being.

RHEUMATOID ARTHRITIS (Adjunctive Therapy—in severely disabling forms, particularly when accompanied by depression): 9 to 12 mg. daily for 3 days, then 6 mg. daily, reducing further to 3 mg. daily on signs of improvement. If a conventional antiarthritic agent is used, lower doses of each are indicated.

CAUTION

Certain circumstances should be watched carefully when using CATRON.

DRUG POTENTIATION—The list of drugs which CATRON potentiates is not yet complete. CATRON should not be used concomitantly with any other drug unless, (a) it has been ascertained that the two drugs bear no qualitative relationship, or (b) potentiating action is being sought, as may be the case with tranquilizing drugs including reserpine and the phenothiazines, and with the amphetamines, barbiturates and hypotensive agents.

HYPOTENSIVE EFFECT—All normotensive patients receiving CATRON, but especially elderly patients, should be warned about the possibility of orthostatic hypotension during the initial period of higher dosage. In the few instances where this may occur, lowering of the dose will usually permit continuation of therapy.

COLOR VISION—A reversible red-green color defect has been reported in a few patients, chiefly hypertensives, on ex-

Psychoactive Agent

- Brightens mood, diminishes apathy and confusion, curbs symptoms of withdrawal, self-pity, inadequacy, despair.[1,2]
- Acts selectively on brain at doses having little or no effect on liver.[5-7]
- Valuable in depressions associated with chronic diseases such as angina pectoris,[8] severe rheumatoid arthritis.[9]

For detailed information, request Brochure No. 19, CATRON

tended therapy with CATRON. Discontinue the drug if such changes occur.

ANIMALS, NEUROLOGIC SIGNS—In toxicity studies with animals, a neurologic syndrome has been observed characterized by tremors, muscle rigidity and difficulty in locomotion. Although extensive clinical experience has not shown such reactions to be a problem in humans in recommended dosage, should a similar neurologic disturbance occur, the possibility of drug action should be considered.

SIDE EFFECTS—Major side effects requiring cessation of therapy are infrequent. Other side effects—constipation, delay in starting micturition, increased sweating, hyperreflexia, ankle edema, blurring of vision, dryness of the mouth—are usually readily controlled by lowering the dosage. Rash, observed in a few patients, cleared up rapidly upon discontinuing therapy.

WARNING: Pharmacologic studies show that with proper dosage CATRON will inhibit monoamine oxidase in the brain without influencing this enzyme in the liver. This is in contrast to previous inhibitors, which depress monoamine oxidase activity in the liver before affecting this enzyme in the brain.

Although the evidence suggests that serious life-threatening hepatitis seen with other MAO inhibitors should not occur with CATRON in the recommended dosage, it has been reported on rare occasion with dosages in excess of the recommended levels.

The Following Precautions are Recommended:

1. In all instances daily dose should not exceed 12 mg.
2. Reduce daily dose as soon as response is established, usually in a matter of 1 to 2 weeks.
3. Do not prescribe to a patient more than sixteen 6 mg. tablets or thirty-two 3 mg. tablets of CATRON at one time.
4. Patient should return for observation before additional CATRON is prescribed. For this reason, prescriptions for CATRON should be marked, "not refillable."
5. Perform regular liver function tests.
6. Do not use the drug in patients with a history of viral hepatitis or other liver abnormalities.

CATRON is the original brand of β-phenylisopropyl hydrazine. It is supplied as the hydrochloride in tablets of 3 mg. and 6 mg., bottles of 50.

(1) Agin, H. V.: The Use of JB-516 (CATRON) in Psychiatry, Conference on Amine Oxidase Inhibitors, New York Academy of Sciences, Nov. 20-22, 1958. (2) Bercel, N. A.: A Pharmacologic Approach to the Study of the Mind, Springfield, Ill., Charles C Thomas, 1959, in press. (3) Kinross-Wright, J.: Panel Discussion of Psychic Energizers, *ibid.* (4) Kinross-Wright, J.: Experience with JB-516 (CATRON) and Other Psychochemicals in Clinical Practice, Conference on Amine Oxidase Inhibitors, New York Academy of Sciences, Nov. 20-22, 1958. (5) Horita, A., and Parker, R. G.: Comparison of Monoamine Oxidase Inhibitory Effects of Iproniazid and Its Phenyl Congener, Proc. Soc. Exper. Biol. & Med. 99:617, 1958. (6) Horita, A.: *Beta*-Phenylisopropylhydrazine, A Monoamine Oxidase Inhibitor, Fed. Proc. 17:379, 1958. (7) Horita, A.: The Pharmacology of the Monoamine Oxidase Inhibitors, in A Pharmacologic Approach to the Study of the Mind, Springfield, Ill., Charles C Thomas, 1959, in press. (8) Kennamer, R., and Prinzmetal, M.: Treatment of Angina Pectoris with CATRON (JB-516), Am. J. Cardiol. 3:542, 1959. (9) Scherbel, A. L., and Harrison, J. W.: The Effects of Iproniazid and Some Other Amine Oxidase Inhibitors in Rheumatoid Arthritis, Conference on Amine Oxidase Inhibitors, New York Academy of Sciences, Nov. 20-22, 1958.

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Milontin

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Celontin

Kapseals (methsuximide, Parke-Davis) 0.3 Gm., bottles of 100.

Literature supplying details on dosage and administration available on request.

*Carter, S.: *M. Clin. North America* 315 (March) 1953.

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NEWSLETTER

AMERICAN ACADEMY OF NEUROLOGY

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A. L. Sahs, M.D., President-Elect
Joseph M. Foley, M.D., Vice-President
Robert Utterback, M.D., Secretary
Charles M. Poser, M.D., Treasurer

SEPTEMBER 1959

ANA Adds Fifteen to its Membership Roster Fifteen candidates were elected members of the American Neurological Association at its Eighty-fourth annual meeting held in Atlantic City, June 15-17, 1959. Elected to active membership were: David B. Clark, Robert Fishman, Eli S. Goldensohn, Howard Krieger, William M. Landau, Tiffany Lawyer, Lewis L. Levy, Leo Madow, Kenneth R. Magee, John S. Meter, Lewis P. Rowland, and H. Edward Yaskin; to associate membership: William S. Battersby and Irving H. Wagman. Abraham Mosovich was elected to Corresponding membership. For a résumé of this meeting of the ANA, see the August 1959 Newsletter.

Queen Square Centenary To Be Celebrated in 1960 From Macdonald Critchley comes the announcement that the National Hospital, Queen Square, London, will be celebrating its centenary in 1960 on June 20 through June 25. The occasion will be marked by neurohistorical presentations, as well as by a wide range of social functions. Personal invitations will shortly be sent to every former student and house officer who has ever worked or trained at the hospital. In addition, the hospital will be extending a most cordial welcome to neurologists, neurosurgeons, and others to participate in these centennial activities. An ad hoc notice will be forwarded in due course, not only to individuals who have studied at Queen Square, but also to all official neurological and neurosurgical societies. For details, apply to Dr. Macdonald Critchley, National Hospital, Queen Square, London W. C. 1.

UCP To Meet in Miami The 1959 annual scientific session of United Cerebral Palsy will be held in Miami on Saturday, November 21, 1959, in conjunction with the annual meeting of the Society. The main topic of the scientific program is "Sensory Disorders of Patients with Cerebral Palsy, Including Disorders of Perception and Learning." Further details on the meeting may be obtained from Brewster S. Miller, Director of Research, UCP Research and Education Foundation, 321 West 44th Street, New York 36....Roger S. Firestone, President of United Cerebral Palsy, has been appointed to the National Advisory Council of the National Institute of Neurological Diseases and Blindness. The appointment

is for a four-year period to begin October 1, 1959. Mr. Firestone is President of the Firestone Plastics Company and Director of the Firestone Tire and Rubber Company.

EEG Society Organized in Mexico Announcement has been made of the organization of the Mexican Society of Electroencephalography (Sociedad Mexicana de Electroencefalografia). The officers of the new society are: Julio Hernandez Peniche, President; Carlos Gunther Strecker, Secretary; and Pedro Ortiz Estrada, Treasurer....The newly created society, through its President, Dr. Peniche, sends friendly greetings to the members of the AAN.

Neurology Section Established at Syracuse The Upstate Medical Center of the State University of New York at Syracuse announces the organization of a new section of neurology, under the direction of Philip E. Duffy. The program is approved by the American Medical Association for residency training. Applications for residency training or for a single position as instructor should be forwarded to Dr. Philip E. Duffy, 150 Marshall Street, Syracuse.

Postgraduate Course Offered in Cerebral Palsy A postgraduate practical course in cerebral palsy is offered to physicians, therapists, and nurses (October 5 to December 4, 1959) by the Department of Physical Medicine and Rehabilitation (Robert C. Darling, professor and department head), of Columbia University's College of Physicians and Surgeons. The purpose of the program is to acquaint potential leaders in cerebral palsy with basic knowledge of this field: to review the present status of practical therapy, including its medical, social, educational, and psychological aspects and to point out the controversial features of our present understanding of these problems. The course will consist of lectures, seminars, demonstrations, and practical clinical training. The physicians' course is for three weeks, October 5-23, 1959, the fee being $100. The course for nurses and therapists lasts for nine weeks, October 5 to December 4, 1959, the fee being $210....Further information may be obtained from: Postgraduate Course in Cerebral Palsy, College of Physicians and Surgeons, 630 West 168th Street, New York 32.

Preliminary Plans Made for WORLD NEUROLOGY Journal In Minneapolis, August 3-4, preliminary plans and agreements were blueprinted for the publication of WORLD NEUROLOGY, the official journal of the World Federation of Neurology. Mr. L. M. Cohen, President of Modern Medicine Publications, and Publisher of NEUROLOGY, has agreed to publish this new international monthly, the first issue to appear about July 1960. Dr. Charles M. Poser,

Medical Executive Officer of the World Federation of Neurology, with headquarters in Antwerp, Belgium, has been elected Editor-in-Chief. He will be assisted by two associate editors, a working editorial board well-dispersed geographically, and a group of consulting editors representing many countries. The purpose of the journal is to provide timely review articles and original articles of international interest in four languages. WORLD NEUROLOGY will also serve as a medium of exchange throughout the world of neurologic information and news and as a source for the location of scientific data, laboratory specimens and literature; the WFN Newsletter will be incorporated into the journal....Inquiries should be addressed to Dr. Charles M. Poser, Medical Executive Officer, World Federation of Neurology, 59 rue Philippe Williot, Berchem-Anvers, Belgium.

British Neuropathologists Convene in Cambridge Under the direction of William McMenemey (Maida Vale), the Neuropathological Club, which is the British counterpart of the American Association of Neuropathologists, held its annual meeting at the School of Medicine at the University of Cambridge (July 17-18, 1959). The sessions were conducted in a lively and informal fashion. Many noted foreign guests attended. Among the program highlights was a paper by J. N. Cumings (London) on the application of electrophoresis to the protein components of cerebral tissues; a presentation by B. P. Hughes (Cambridge) on the electrophoresis of some muscle proteins in starch gels, showing a relatively new and promising technic; and a study by P. O. Yates on the cell tissues in birth injuries to the neck of the premature and neonate. Also, Cambridge's anatomy professor, A. Hughes, presented a motion picture of growing neurons, and P. Sourander (Göteborg) demonstrated through tissue culture studies important factors in the life cycle of the toxoplasma....Charles M. Poser, Medical Executive Officer of the WORLD FEDERATION OF NEUROLOGY, who attended the meeting, reports, "The British Neuropathological Club is a sharp and active group renowned in the application of the latest technics such as electrophoresis, electronmicroscopy, tissue culture, as well as the more classical techniques of neuropathology."

Briefs Percival Bailey has retired as Distinguished Professor of Neurology and Neurosurgery at the University of Illinois to become Director of Research at the Illinois State Psychiatric Institute, Department of Public Welfare, 1601-59 West Taylor Street, Chicago 12....Howard P. Rome is the newly elected secretary of the Section on Nervous and Mental Diseases of the American Medical Association. The Section reaches its centenary this year....On June 12, 1959, Senator Lister Hill of Alabama turned the first earth in the ground-breaking ceremonies for the $7.3 million building for the National Library of Medicine to house the

world's greatest collection of medical literature. It will be situated on the campus of the National Institutes of Health in Bethesda. The new edifice is scheduled to be completed by June 1961. The National Medical Library is three years old in name only. It is the successor of the Armed Forces Medical Library and the Army Medical Library, which, in 1922, succeeded the famed library of the Surgeon General's office created by William A. Hammond, one of the founders of American neurology....An American edition of Professor Georges Guillain's, J.-M. Charcot, His Life-His Work, edited and translated by Pearce Bailey, has been published by Paul B. Hoeber, Inc., 49 East 33rd St., New York 16.

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You'd give him the world, if you could. A free and happy world to learn in. A world of peace, where he can grow up, free of fear.

But peace takes more than *wanting*, these days. It takes a lot of doing, too. And peace costs money.

Money for strength to keep the peace. Money for science and education to help make peace lasting. And money saved by individuals, to keep our economy sound.

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Tablets‡, 5 mg., 10 mg. and (primarily for use in psychiatry) 25 mg. —for convenient manipulation of dosage.

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Ampuls‡, 2 cc. (5 mg./cc.)—for immediate control of disturbed patients.

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1. Lipton, A. A.: Effect of meprobamate on patients in intensive psychotherapy. Dis. Nerv. System *19*:487, Nov. 1958. 2. Laird, D. M., Angelo, J. N. and Hope, J. M.: Evaluation of meprobamate (Miltown) in treatment of hospitalized schizophrenic patients. Dis. Nerv. System *18*:346, Sept. 1957. 3. Hollister, L. E., Elkins, H., Hiler, E. G. and St. Pierre, R.: Meprobamate in chronic psychiatric patients. Ann. New York Acad. Sc. *67*:789, May 9, 1957.

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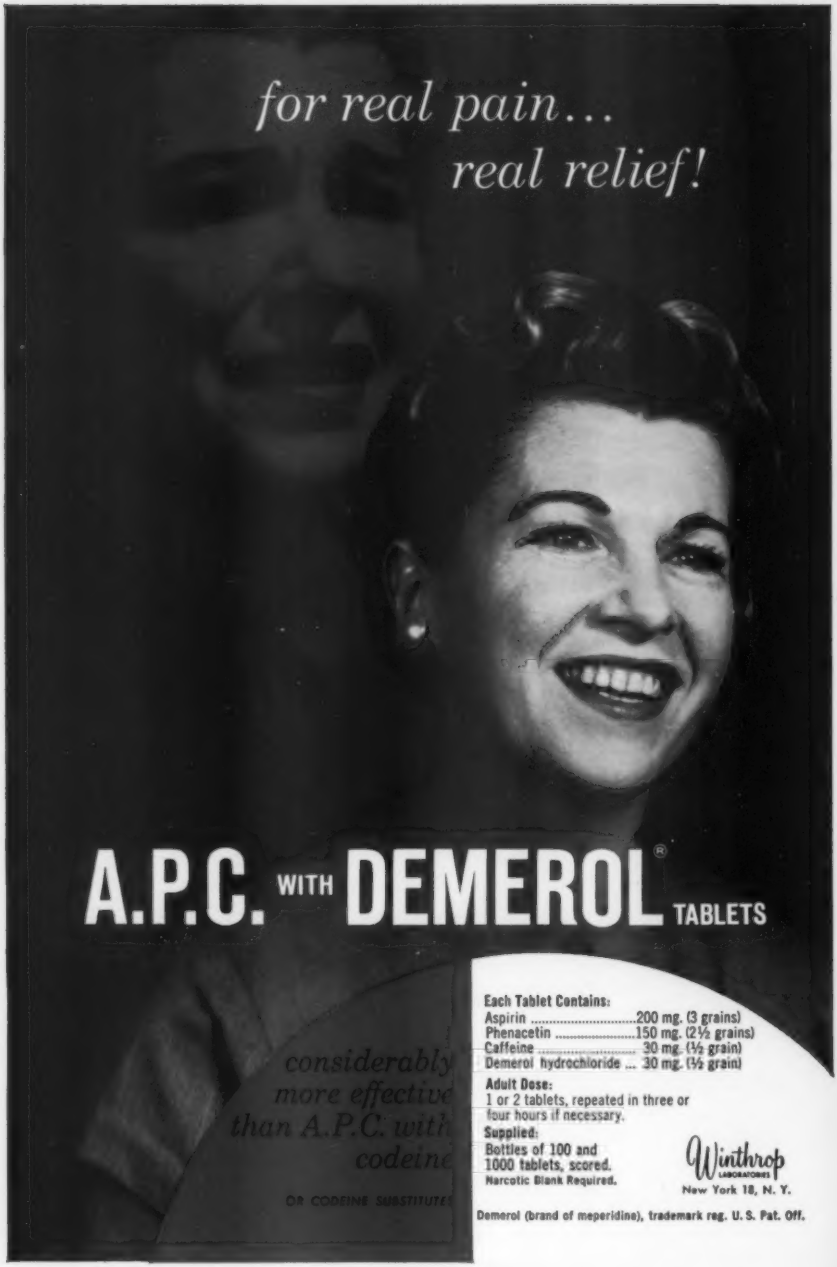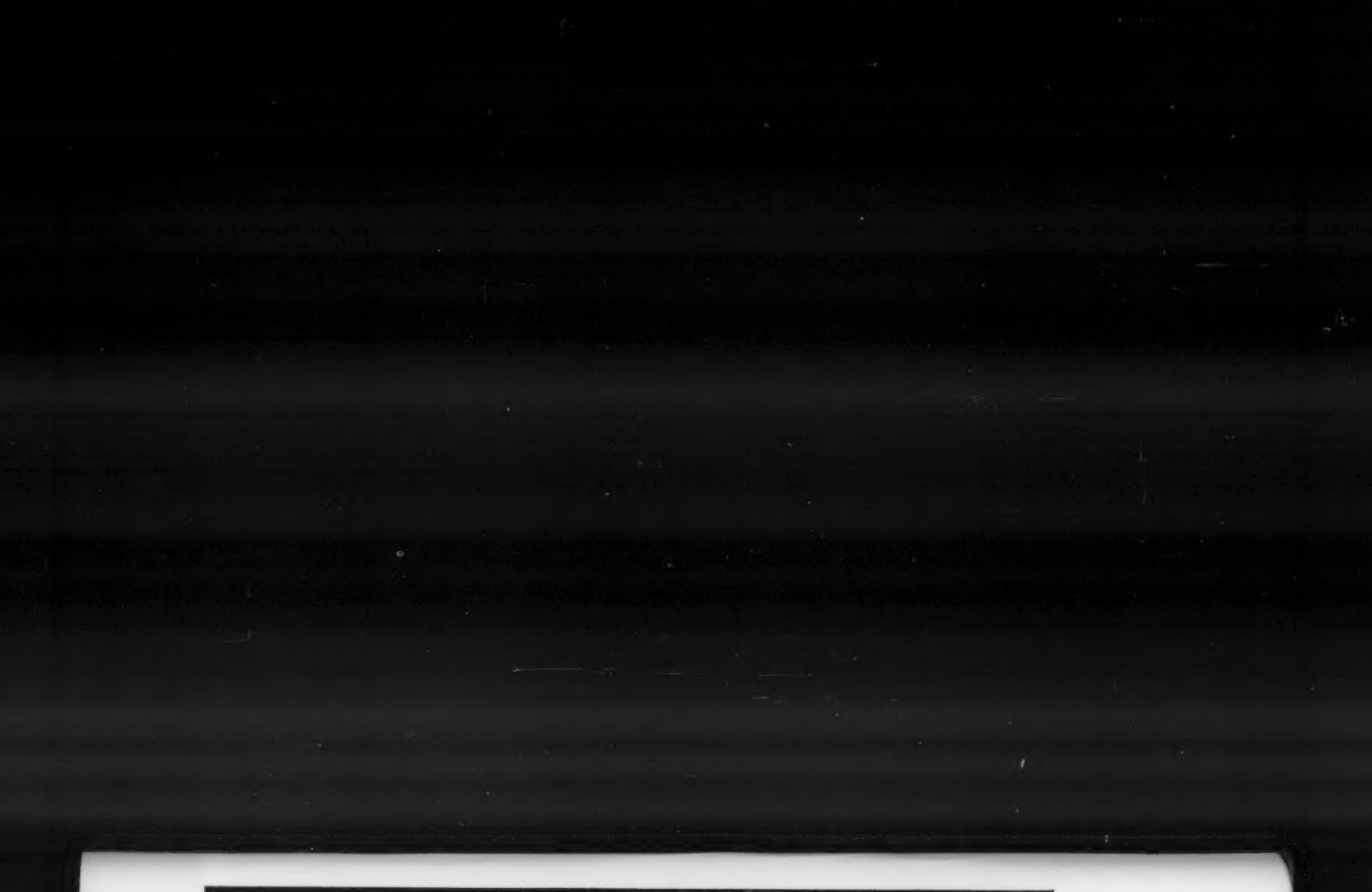
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